Chapter 3

Federal Agency Assessment and Regulation of Carcinogens

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This chapter describes the major statutes and agency actions regulating human exposure to carcinogens. Most of these statutes do not single out carcinogens for specific consideration, but merely regulate them as a species of toxic substance. The exception to this is the Food, Drug, and Cosmetic Act (FDCA), which, in its "Delaney clause, " prohibits the intentional use of carcinogens as food or color additives. In the Clean Water Act (CWA), the Toxic Substances Control Act (TSCA), and the Resource Conservation and Recovery Act (RCRA), Congress did not specify any particular type of regulatory action for carcinogens beyond what is required for other toxic effects. But carcinogens were mentioned as agents of particular congressional concern.

These laws established different regulatory mechanisms and specified the considerations on which the agencies are to make regulatory decisions and the range of allowable discretion. Under some provisions of FDCA, TSCA, and the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), premarket review of a substance is required before it can enter into commerce. Most of the statutes, including other provisions of FDCA, TSCA, and FIFRA, however, provide for postmarked regulation of substances after they have been in commerce and people have been exposed to them. Once a health problem has been identified an agency would be required to either propose a regulation based on that finding, such as, under the Clean Air Act (CAA), CWA, the Safe Drinking Water Act (SDWA), or the Occupational Safety and Health Act, or establish this fact in court, and seek a judicial remedy on that basis. Some sections of FDCA and the statutes administered by the Consumer Product Safety Commission (CPSC) follow this approach,

To regulate carcinogenic substances, Federal agencies follow rulemaking procedures that are set by their statutes or those established by the Administrative Procedure Act (5 U.S.C. 553), which may be either informal or formal. Under the latter procedures the agency must issue a "Notice of Proposed Rulemaking" (NPRM), which describes the proposed regulation, explains the basis for the proposal, and announces an opportunity for comment by interested parties. After written comments are received, a hearing maybe held to obtain public comments. After considering the comments, a final rule is published in the Federal Register. The proposal may also be altered or withdrawn. Formal rulemaking procedures differ from informal ones by the nature of the evidence presented during the comment period, the opportunity for cross-examination of witnesses in hearings, which may resemble the proceedings in a court of law, and, some argue, closer scrutiny by the courts.

The nature of the evidence an agency may consider as the basis for carcinogen regulation reveals various attitudes toward the acceptability of risk. In the most general terms, regulatory approaches are of several types:

- risk-based, such as the Delaney clause of the FDCA which requires the ban of a food additive shown to cause cancer in humans or in animal tests;
- *technology-based,* which might require the use of "best available technology" (BAT) or "best practical technology" (BPT) to control emissions from a particular source; or
- *risk-benefit or cost-benefit balancing,* which could permit the consideration of competing health risks and benefits—such as in the case of cancer-causing drugs used to treat fatal illnesses—or the costs of control and other economic impacts.

There are also different types of agency actions. Some statutes set exposure standards for air (e.g., the Occupational Safety and Health Administra-

tion's permissible exposure limits) or water (e.g., exposure limits in water under SDWA). Others require emission standards for air (under CAA) or water (under CWA). Under other statutes, Federal agencies issue rules concerning the "safe use" of a product (under the Consumer Product Safety Act (CPSA), FDCA, or FIFRA), and some permit or require outright banning of substances or products containing them (under FDCA, FIFRA, and CPSA).[1]

Agency actions in trying to control carcinogens have been as varied as the statutes under which they work. Some agencies have regulated as many as 191 potential carcinogens (under the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA, or Superfund) and *29* carcinogenic chemical classes (of the *65* classes required to be regulated in a judicial order under CWA), while others have regulated only a few (e.g., under the authority of CAA, the Environmental Protection Agency (EPA) has regulated 4 carcinogens in 16 years). For the most part, it appears that the agencies do not act quickly when they learn that a substance is carcinogenic, since there is usually a considerable delay between the time when the outcome of human epidemiologic studies or animal bioassays becomes known and final regulations are published, as well as between the issuing of proposed and final rules.

[1]This background paper only describes the nature of the standards or regulations issued, and does not discuss implementation and enforcement of these regulations.

OSHA REGULATORY ACTIONS

The Occupational Safety and Health Act of 1970 established the Occupational Safety and Health Administration (OSHA) and the National Institute for Occupational Safety and Health (NIOSH). OSHA is a regulatory agency which, among its other duties, issues and enforces regulations that limit exposure to carcinogens in the workplace. NIOSH is a research agency that has supported epidemiologic and toxicologic research and makes recommendations to OSHA concerning changes in occupational health standards.

The act provides three statutory mechanisms for establishing standards for protection from hazardous substances:

1. Section 6(a), which authorized OSHA to adopt the standards already established by Federal agencies or adopted as national consensus standards, as "startup standards" during the first 2 years after the act went into effect. The original source for most of these standards was the list of threshold limit values (TLVs) published by a professional society, the American Conference of Government Industrial Hygienists (ACGIH).
2. Section 6(b), which authorizes OSHA to issue new permanent exposure standards in rulemaking proceedings.
3. Section **6(c),** which authorizes OSHA to issue emergency temporary standards that require immediate action to reduce a workplace hazard when employees are exposed to a "grave danger." A section **6(c)** action also initiates the process of establishing a permanent standard under 6(b).

The standards issued may require monitoring and medical surveillance, modification of workplace procedures and practices, requirements for recordkeeping, and new or modified Permissible Exposure Limits (PELs), which are the maximum concentrations of toxic substances permitted in the workplace air.

Standards adopted under section 6(b) must "adequately assure" that "to the extent feasible . . . no employee will suffer material impairment of health or functional capacity even if such employee has regular exposure to the hazard dealt with by such standard for the period of his working life." Interpreting this mandate has been at the center of legal disputes around OSHA's regulation of toxic workplace exposures. In a major decision, the Supreme Court invalidated OSHA's 1978 benzene standard, ruling that OSHA had to demonstrate that exposure at the current permis-

sible levels presents a "significant risk" to workers before lower exposure standards can be issued.

Prior to this decision, OSHA had prepared quantitative risk assessments concerning substances it regulated. The first one of these was prepared in 1976 for the proposed standard regulating coke oven emissions (118). In the case of benzene, however, OSHA concluded that because of the uncertainties, it would not conduct quantitative risk assessment. The subsequent legal battle involved whether OSHA would be required to conduct such assessments. Following the benzene decision, OSHA has conducted quantitative risk assessments to demonstrate that current permissible exposure levels present a "significant risk" to workers. The first quantitative risk assessment conducted after the Supreme Court decision involved worker exposure to arsenic.

In 1971, OSHA adopted exposure limits on approximately 400 specific chemical substances as startup standards as required by section 6(a). Although these exposure limits had been developed primarily to protect against noncarcinogenic toxicities, some of the substances are also carcinogens.

From 1972 to 1986 OSHA issued more stringent health standards covering 22 carcinogens (see table 3-1). Nine of OSHA's final actions on health standards established new PELs and other requirements on individual carcinogens (asbestos (1972), vinyl chloride *(1974),* coke oven emissions (1976), benzene (1978), 1,2-dibromo-3-chloro-propane (DBCP) (1978) arsenic (1978), acrylonitrile (1978), ethylene oxide (1984), and a second regulation on asbestos (1986)). One OSHA standard regulating a group of "14 carcinogens" did not institute or change a PEL, but created new requirements for work practices and medical surveillance for this group of carcinogens and mandated use of "closed system operations. "[2] One final action in 1983 clarified that asphalt fumes, which contain known carcinogens, are not regulated under the OSHA startup standard for coal tar pitch volatiles (219). The reason for this is that asphalt fumes contain a significantly lower percentage of the polyaromatic hydrocarbons listed in the coal tar pitch volatile standard (278).

Thus, OSHA has used two different approaches for limiting exposures: setting permissible exposure limits and requiring specific process technology and procedures. The latter was used for the group of 14 carcinogens and, while a permissible exposure limit for coke oven emissions was set, the standard also included relatively specific requirements concerning the types of engineering controls that were to be used. For either approach, OSHA has mandated the use of engineering controls as the primary method of compliance, in contrast to use of gas masks and respirators (219). The focus on "closed systems" and stringent work procedures instead of setting PELs for the 14 carcinogens reflected the facts that closed system operations were possible and that many of these chemicals had readily available substitutes.

OSHA has also issued "generic" standards that apply to large groups of chemical exposures. Two of these affect workers exposed to carcinogens—the Hazard Communication Standard and the Access to Medical and Exposure Records Standard. The former requires that hazardous chemicals in the workplace be labeled, that employers set up training programs for workers on chemical hazards in the workplace, and that chemical manufacturers prepare and that employers keep copies of material safety data sheets for hazardous chemicals. The standard defines hazardous chemicals to include carcinogens (29 CFR 1910.1200).

The Access to Medical and Exposure Records Standard *(29* CFR 1910.20) requires that employers allow employees and their representatives access to medical and exposure records and requires that these records be preserved for specified time periods. However, the standard does not require that employers conduct exposure monitoring or medical surveillance. The standard does require that if the employer conducts such monitoring or surveillance that records be kept and made available to workers. Again, exposures to carcinogenic chemicals are covered by this standard.

[2] According to OSHA's preamble to the final rule, 13 of these 14 substances were derived from ACGIH Appendix A. Alpha-naphthylamine was added because it is often found together with beta-naphthylamine. Dimethyl sulfate appears in the ACGIH appendix but was excluded for inadequate documentation of carcinogenicity (272).

Table 3-' .—OSHA Regulation of Carcinogens

Substance	Type of evidence	Petition	NPRM	Final	Court action challenge
2-Acetylaminofluorene	Animal, 6 species—mice, rats, rabbits, dogs, fowl, hamsters	1-4-73 OCAW/HRG)	9-7-73[c]	-29-74	"Fourteen Carcinogens"[a]
Acrylonitrile	Human; animal, species—rats	3-78 (Manufacturing Chemists Assoc.)	1-17-78[b]	10-3-78	—
-Aminobiphenyl	Human; animal, 3 species—mice, dogs rabbits	1-4-73 (OCAW/HRG)	9-7-73[b]	1-29-74	[a]
Asbestos I)	Human	—	1-12-72; 10-9-75	6-7-72 —	1972 standard affirmed—*Industrial Union Dept., AFL-CIO* v. *Hodgson*, 499 F.2d 467 (D.C. Circuit, Apr. 15, 1974)
Asbestos (II)[b]	Human	—	4-10-84	6-20-86	Standard lowered from 2 to 0.2
I)	Human-suggestive evidence	—	5-27-77	2-10-78	Vacated, *American Petroleum Institute* v. *OSHA*, 581 F.2d. 493 (5th Cir., Oct. 5, 1978) & *Industrial Union Department, AFL-CIO* v. *American Petroleum Institute*, 448 U.S. 607 (Supreme Court, July 2, 1980)
Benzene (II)	Animal, 2 species—mice, rats	4-83	12-10-85	—	—
Benzidine	Human; animal, 4 species—mice, rats, dogs, hamsters	1-4-73 OCAW/HRG	9-7-73[b]	1-29-74	Carcinogens"[a]
Beryllium	Human-suggestive evidence; animal, 3 species—rats, rabbits, monkeys	—	○ 7-75	—	
bis-Chloromethyl ether	Animal, 2 species—mice, rats	1-4-73 OCAW/HRG	9-7-73[b]	1-29-74	"Fourteen Carcinogens"[a]
Coal tar pitch volatiles	—	1980, 4-8 (Asphalt Institute)		1-21-83	Petroleum derived asphalt fumes removed from definition
Coke oven emissions	Human	—	7-31-75	10-22-76	Affirmed, *American Iron & Steel Inst.* v. *OSHA*, 577 F.2d 825 (3d Cir., 3-28-78)
1,2-Dibromo-3-chloro-propane	Animal, 2 species—rats, mice	8-23-77 (OCAW request)	11-1-77	3-17-78	—
1,2 Dibromoethane (EDB)	Animal, 2 species—mice, rats	9-81, 2-3-84 (Teamsters)	10-7-83	—	—
3,3'-Dichlorobenzidine	Animal, 3 species—rats, mice, hamsters	1-4-73 (OCAW/HRG)	9-7-73[b]	1-29-74	"Fourteen Carcinogens"[a]
4-Dimethylaminoazobenzene	Animal, 4 species—rats, mice, dogs, trout	1-4-73 (OCAW/HRG)	9-7-73[b]	1-29-74	"Fourteen Carcinogens"[a]

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Table 3.1 .—OSHA Regulation of Carcinogens—Continued

Substance	Type of evidence	Petition	NPRM	Final	Court action challenge
Ethyleneimine	Animal, 2 species–rats, mice	—	9-7-73[b]	1-29-74	"Fourteen Carcinogens' [a]
Ethylene oxide	Human, strongly suggestive evidence, animal, 1 species–rats	8-31-81 (HRG/AFSCME)	4-21-83	6-22-84	HRG et *al v Auchfef* 554 F Supp 242 (D C Dist Ct 1-5-83) & 702 F 2d 1150 (D C Cir 3-15-83)
Formaldehyde	Animal, 2 species–mice, rats	10-26-81 (UAW)	12-10-85	—	—
Inorganic arsenic	Human	—	1-21-75	5-5-78	Affirmed, *ASARCO Inc. et al v OSHA 746* F 2d 483 (9th Cir 9-13-84)
Methyl chloromethyl ether	Inconclusive–contains bls-chloromethyl ether	—	9-7-73[b]	-29-74	"Fourteen Carcinogens' [a]
4,4- Methylenebw (2-Chloroanlhne) (M BOCA)	Animal, 2 species–rats, mice	—	9-7-73[b] 2-3-75	-29-74	'Fourteen Carcinogens a –vacated 12-17-74
alpha- Naphthylamme	Found m association with beta-Naphthylamme & has carcinogenic derivatives	·	9-7-73[b]	-29-74	'Fourteen Carcinogens' [a]
beta-Naphthylamme	Human, animal, 5 species–rats, mice, hamsters, dogs, monkeys	1-4-73 (OCAW/HRG)	9-7-73[b]	*1-29-74*	' 'Fourteen Carcinogens' [a]
4- Nitroblphenyl	Animal, 1 species–dog, forms 4-Ammo-dlphenyl which is carcmogemc m humans	1-4-73 (OCAW/HRG)	9-7-73[b]	*1-29-74*	*"Fourteen* Carcinogens' [a]
beta-Proplolactone	Animal, 3 species–mice, rats, hamsters	1-4-73 (OCAW/HRG)	9-7-73[b]	*1-29-74*	"Fourteen Carcinogens' [a]
N- Nitrosodlmethylamlne	Animal, 6 species–rats, mice, rabbits, hamsters. guinea pigs, fish	1-4-73 (OCAW/HRG)	9-7-73[b]	1-29-74	"Fourteen Carcinogens' [a]
Trichloroethylene	Animal, 1 species–mice, data inconclusive	—	10-20-75	—	—
Vinyl chloride	Human, animal, 3 species–rats, mice. hamsters	3-14-74 (UnNed Rubber Workers, IUD. OCAW)	4-5-74(1)	10-4-74	Affirmed, Society of the *Plastics Industry Inc v OSHA, 509* F 2d 1301 (2d Cir. 1-31-75)

[a]Standards were issued simultaneously for 14 Carcinogens Initiallyissuedas **emergency temporary standards 2 of the 14 were struck** down in **Dry** *Color Manufacturing v Department of Labor,* 486 **F 2d** 98 **(3rd** Circuit. **Oct** 4, 1973) Final standards were then issued **The Court upheld all** final **standards except** 44 Methylenebis (2-chloroaniline) in *Synthetic Organic Chemical Manufacturers Association v Brennan* 506 F 2d 385 **(3rd Circuit. Dec** 17, 1974) **The** ethyleneimine **standard was** affirmed in *Synthetic organic Chemical Manufacturers Association v Brennan, 503* **F 2d 1155 (3d** Cir 8.26-74)

[b]Also an emergency temporary standard

SOURCES. OSHA response to OTA request, ***Federal Register*** **notices cited** in **the agency response,** ***Preventing Illness and Injury In the Workplace,*** OTA, 1985, "Summary of OSHA Regulations & NIOSH Recoin mendations for Occupational Safety & Health Standards, 1986" published **in** MMWR vol 35, No 1S

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Both standards are important. The Hazard Communication Standard, in particular, has led to a major effort devoted toward updating material safety information and communicating this information to workers. In addition, OSHA is now in the process of expanding the scope of the Hazard Communication Standard to all industries. The standard currently applies to the manufacturing sector, including chemical companies that supply the relevant hazard information, but nonmanufacturing industries are not required to implement the program. The effects of these standards on actual exposures in the workplace, however, are indirect. OSHA is still working on standards setting specific exposure levels and mandating other types of health and safety activities, even for chemicals covered by the Hazard Communication and Access to Records standards.

OSHA's regulation of carcinogens has been controversial. Of nine final actions on individual carcinogens, seven have resulted in court challenges: on asbestos (twice), vinyl chloride, coke oven emissions, benzene, arsenic, and ethylene oxide. The rules on DBCP and acrylonitrile were not challenged as final standards. For the standard regulating 14 carcinogens as a group, the ethyleneimine and 4,4-methylenebis(2-chloroaniline) (MBOCA) standards were challenged. In all, two permanent standards were struck down as a result of those challenges: MBOCA and benzene. Thus, standards are in effect for 20 of the 22 chemicals regulated as carcinogens.[3]

In the 16 years since the OSH Act passed, NIOSH, part of the Centers for Disease Control, issued 93 recommendations concerning carcinogens. As summarized in table 3-2, these consisted of *32* criteria documents, 6 revised criteria documents, 19 current intelligence bulletins, 10 special hazard reviews, 3 health hazard alerts, 1 occupational hazard assessment, and a list of 22 substances (including the "14 carcinogens") for which recommendations were made in testimony presented in 9 OSHA regulatory proceedings. Criteria documents and regulatory testimony identify substances that pose potential health problems and recommend exposure levels to OSHA. The other documents represent NIOSH efforts to communicate research findings and warnings to workers and employers.

NIOSH has changed its policy on criteria documents. While a large number were produced in the early to mid-1970s, OSHA criticized the quality of the documents and rarely responded (see table *3-2).* Starting under NIOSH Director Anthony Robbins, the agency placed greater emphasis on epidemiologic studies and health hazard evaluations (evaluations of reported worker health problems in particular workplaces), and has reemphasized production of criteria documents. From 1971 to 1980, NIOSH issued 77 recommendations, about 7.7 per year, while from 1981 to 1986, it has issued 16 criteria documents, current intelligence bulletins, or special hazard alerts, about *2.6* per year.

In all, the NIOSH recommendations cover *71* different chemicals or processes that were determined by NIOSH to be carcinogenic. Of these 71, OSHA has responded by issuing health standards for 21 chemicals or processes: asbestos (twice), arsenic, coke oven emissions, vinyl chloride, benzene, acrylonitrile, ethylene oxide, and the 14 carcinogens regulated together. However, for two chemicals (benzene and MBOCA), the OSHA standard was vacated by the courts. Thus 19 chemicals and processes have actually been regulated for carcinogenic effects based on NIOSH recommendations. OSHA regulated one chemical, DBCP, for carcinogenic effects although the NIOSH recommendation was only based on adverse toxic effects. As of early 1987, OSHA has an active proposal pending on benzene exposures. However, no activity is currently being considered for MBOCA exposures, although this substance is still being imported and used in the United States.

The remaining sO chemicals or processes have not been the subjects of final OSHA 6(b) standards, although many are being regulated under 6(a) standards that were adopted in 1971 based on recommendations concerning noncarcinogenic effects. Of these 50 chemicals or processes, OSHA has proposed regulations for 4: formaldehyde, ethylene dibromide, trichloroethylene, and beryllium, although the latter two were proposed in

[3] A recent report of the Administrative Conference of the United States discusses OSHA rulemaking. See (1).

Table 3-2.—NIOSH Identification of Carcinogens

Substance	Type of recommendation	Date	OSHA proposed or final action	Type of evidence
2-Acetylaminofluorene	T	9-73	1-29-74	Animal
Acrylonitrile	CD	9-77	10-3-78	Animal, human
Aldrin/Dieldrin	SHR	9-78	—	Animal
4-Amlnobiphenyl	T	9-73	1-29-74	Human
Arsenic	CD	9-74	—	Human (nonconclusive)
	CD(rev)	6-75	5-5-78	Human
Arsine	ClB	8-79	—	Human[a]
Asbestos	CD	1-72	1-21-75"	Human
	CD(rev)	12-76	—	Human
	T	6-84	6-20-86	Human
Benzene	CD	7-74	—	Human (limited evidence)
	CD(rev)	8-76	—	Human
	T	7-77	2-10-78**	Human
	T	3-86	12-10-85*	Human
Benzidine	T	9-73	1-29-74	Human
Benzidine-based dyes	SHR	11-79	—	Human
Beryllium	CD	6-72	10-17-75"	Animal
	T	8-77	—	Animal, human
bis-Chloromethyl ether	T	9-73	1-29-74	Human
I,3-Butadiene	CIB	2-84	—	Animal, human
Cadmium	CD	8-76	—	Human (toxic effects)
	CIB	9-84	—	Animal, human
Carbon black	CD	9-78	—	Animal
Carbon tetrachloride	CD	12-75	—	Animal
	CD(rev)	6-76	—	Animal
Chloroform	CD	9-74	—	Animal
	CD (rev.)	6-76	—	Animal
Chloroprene	CD	8-77	—	Human
Chromium	CD	12-75	—	Animal, human
Chrysene	SHR	6-78	—	Animal
Coal gasification plants	CD	9-78	—	Animal, human
Coal liquefaction	OHA	3-81	—	Animal, human
Coal tar products	CD	9-77	—	Animal, human
Coke oven emissions	CD	2-73	—	Human
	T	11-75	10-22-76	Animal
DOT	SHR	9-78	—	Animal
2,4-Diaminoanisole	CIB	1-78	—	Animal, human (suggestive evidence)
3,3'- Dichloro-benzidine	T	9-73	1-29-74	Animal
Di-2-ethylhexyl Phthalate (DEPH)	SHR	3-83	—	Animal
4-Dimethylaminoazobenzene	T	9-73	1-29-74	Animal
Dinitrotoluenes	CIB	7-85	—	Animal
Dioxane	CD	9-77	—	Animal
Epichlorohydrin	CD	9-76	—	Animal
	CIB	10-78	—	Animal, human
Ethylene dibromide	CD	8-77	—	Animal
	T	11-83	—	Animal
Ethylene dichloride	CD	3-76	—	Human (toxic effects)
	CD(rev)	9-78	—	Animal
Ethyleneimine	T	9-73	1-29-74	Animal
Ethylene oxide...	SHR	9-77	—	Human (potential)
	T	7-83	6-22-84	Animal, human
Ethylene thiourea	SHR	10-78	—	Animal
Formaldehyde	CD	12-76	12-10-85'	Human (toxic effects)
	CIB	4-81	—	Animal
	T	5-86	—	Animal human (potential)
Foundries	CD	985		Human
Glycidyl ethers	CD	6-78	—	Animal
Hexachloroethane	CIB	8-78	—	Animal
Hydrazines	CD	6-78	—	Animal

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Table 3-2.—NIOSH Identification of Carcinogens—Continued

Substance	Type of recommendation	Date	OSHA proposed or final action	Type of evidence
Isopropyl alcohol	CD	3-76	—	Human[b]
Kepone	CD	1-76		Animal
Methyl chloromethyl ether	T	9-73	1-29-74	Animal
4,4' -Methylenebis-(2-chloroaniline) (MOCA)	T	9-73	1-29-74**	Animal
	SHR	1978	2-3-75*	Animal
Methylene chloride		3-76	—	Human (toxic effects)
	CD	4-86		Animal
4,4-Methylenedianiline	CIB	7-86		Animal, human
Monohalomethanes	CIB	9-84	—	Animal
alpha-Naphthylamine	T	9-73	1-29-74	Human
beta-Naphthylamine	T	9-73	1-29-74	Human
Nickel carbonyl	SHR	5-77	—	Animal
Nickel, inorganic compounds	CD	5-77		Animal, human
4-Nitrobiphenyl	T	9-73	1-29-74	Animal
2-Nitronapthalene	CIB	12-76		Animal (caused by metabolite)
2-Nitropropane	B	4-77		Animal
	HHA	10-80		Animal
N-Nitrosodimethylamine	T	9-73	1-29-74	Animal
O-Dianisidine-based dyes	HHA	12-80	—	Animal, human[c]
O-Tolidine-based dyes	HHA	12-80	—	Animal, human[c]
O-Tolidine	CD	1-74	—	Animal
Phenyl-beta-naphthylamine	CIB	10-76		Animal[d]
Polychlorinated biphenyls	CD	9-77	—	Animal
beta-Propiolactone	T	9-73	1-29-74	Animal
2,3,7,8-Tetrachloro-dibenzo-p-dioxin (TCDD)	CIB	1-84	—	Animal
1,1,2,2-Tetrachloro-ethane	CD	12-76		Animal, human (toxic effects)
1,1,2,2-Tetrachloroethane	CIB	8-78		Animal
Tetrachloromethylene	CD	7-76	—	Human (toxic effects)
	CIB	1-78	—	Animal
Trichlorethylene	CD	6-73	10-20-75* no final action	Human (toxicity data)
	SHR	1-78	10-20-75"	Animal
1,1,2-Trichloroethane	CIB	8-78	—	Animal
Vinyl chloride	CD	3-74	10-4-76	Animal
Vinyl halides	CIB	9-78	—	Animal. human

*Date of notlce of proposed rulemaking (NPRM)
* *Vacated
[a]Based on evidence for arsenic because Arsine metabolizes to inorganic arsenic in the human body.
[b]Carcinogenic effect considered derived from strong-acid in production process, no evidence for carcinogenicity of isopropyl alcohol itself.
[c]Based on evidence for benzidine *because* it converts to benzidine in humans.
[d]Based on evidence for beta-naphthylamine because it metabolizes to beta-naphthylamine in humans,

ABBREVIATIONS. CD = Criteria Document, CIB = Current Intelligence Bulletin; HHA = Health Hazard Alert, OHA = Occupational Hazard Assessment; (rev) = Revised, SHR = Special Hazard Review; T = Testimony to Dept. of Labor

SOURCES: NIOSH/OSHA responses to OTA request including summary of NIOSH Documents for Carcinogenic Agents; "Summary of OSHA Regulations and NIOSH Recommendations for Occupational Safety and Health Standards," published in MMWR vol. 35, No 1S; *Preventing Illness and Injury in the Workplace,* OTA. 1985.

1975 and can now be considered dormant. For the remaining chemicals or processes, no OSHA proposals have been issued.

OSHA'S regulatory agenda has increasingly been set by outsiders, through petitions, court orders, referrals from EPA and congressional directives. The formaldehyde standard involved a petition, a referral from EPA and a court order after OSHA delays. OSHA has also received formal or informal referrals from EPA under section 9 of TSCA, for 4,4'-methylene dianiline (MDA), 1,3-butadiene, chloromethane, MBOCA, toluenediamine, glycol ethers, acetaldehyde, and acrylamide. In the Superfund amendments of 1986, Congress directed OSHA to issue standards on health and safety protection for workers at hazardous waste sites.

During the first 10 years of its existence, OSHA issued 8 final rules, while from 1981 to 1986, OSHA has issued 2 final rules to reduce exposures to specific carcinogens, a rate of 3 years per regulation. On average, 15 months have elapsed be-

tween OSHA's issuance of an NPRM and publication of a final rule on a particular substance. Further, during the first 10 years of OSHA's existence, the time from criteria document to final rule was about 32 months, while during the last 6 years, the average has been about 60 months. There are still a number of regulations yet to be acted on that could modify this last average, which is based on just two final rules. One final rule issued since 1981 was a more stringent regulation of asbestos, previously regulated by OSHA, while the final rule for ethylene oxide was issued under court order (see the discussion of judicial action in app. A). Benzene, first identified as a health hazard by NIOSH in a criteria document in **1974,** was initially regulated in *1978.* That final rule was overturned by the Supreme Court in 1981. Subsequently, NIOSH has issued several revised recommendations (in 1976, 1977, and *1986),* but OSHA has yet to issue a final rule on benzene.

Although OSHA's cancer policy permits the regulation of carcinogens on the basis of animal evidence alone, for the most part the agency has regulated on the basis of human evidence, evidence which in most cases was confirmed by animal evidence. Not considering the 14 carcinogens regulated as a group, OSHA has issued final rules for 8 individual substances based on at least some evidence of human carcinogenicity. DBCP, however, was regulated primarily because it caused infertility in men, although animal carcinogenicity data was available.

Of the "14 carcinogens, " 3 are human carcinogens, 8 are positive in 2 or more species (a number of these 11 carcinogens are positive in 3 to 5 mammalian species), and 1 was positive in a single species. The remaining 2 chemicals (alphanapththylamine and methyl chloromethyl ether) are found in association with other carcinogens on the list of 14 and were themselves thought to pose potential risks. Thus 11 of the 22 chemicals were regulated based partly on human evidence, and most of the animal carcinogens were regulated early in OSHA's history—in the 1974 standard on 14 carcinogens.

MSHA REGULATORY ACTIONS

The Mine Safety and Health Administration (MSHA) regulates the exposure of miners to carcinogens. The Federal Mine Safety and Health Amendments Act **(1977)** consolidated the regulation of mine health and safety under one statute, and transferred responsibility from the Department of the Interior to the Labor Department. Safety and health in coal mines had previously been regulated under the Federal Coal Mine Health and Safety Act of 1969 by the Department of the Interior's Mining Enforcement and Safety Administration (MESA), while safety and health in metal and nonmetal mines had been regulated by MESA under the Federal Metal and Nonmetallic Mine Safety Act of 1966 (150).

Separate standards are issued for surface and underground coal mines and for surface and underground metal and nonmetal mines. For the most part, standards adopt the 1972 and 1973 *rec*ommendations of the ACGIH. Other than in radiation and asbestos, MSHA has found relatively few exposures to carcinogens in mines.

When MSHA's predecessor agency issued the surface coal mining regulations in 1972 it specified that exposures to toxic substances should not exceed those recommended by ACGIH in 1972. At that time only some potential carcinogens in diesel fumes and polychlorinated biphenyls (PCBS) were thought to present possible problems in the surface mining of coal.

For underground coal mining, MSHA's regulations require mines to keep exposures at least as low as the "current" ACGIH recommended exposures, with the idea that the exposure levels would be updated each time ACGIH changed its list of toxic substances. Although MSHA legal staff interpret "current" to be the *1972* list, which was current when the regulations were issued, MSHA staff stated to OTA that inspectors enforce those that are actually current. The issue has not been resolved in part because there have been very few citations. There is debate within the agency over whether it would be in violation of the Administrative Procedure Act for the regulations

to be automatically updated by ACGIH because it would not provide opportunity for the public to comment on the updated exposure levels (190).

Regulations that govern exposure to carcinogens in metal and non-metal mines incorporate by reference the 1973 ACGIH recommendations. In 1978, for metal and non-metal mines, MSHA regulated the 14 carcinogens that had been regulated by OSHA in 1974, and 2 other substances, by restricting their use to approved laboratory conditions and competent personnel (see table 3-3).

Apart from incorporating by reference the ACGIH list of carcinogens, MSHA issued regulations in the late 1970s on asbestos, lowering the permissible exposure level as specified in the 1973 ACGIH list froms fibers to 2 fibers greater than 5 microns in length per cubic centimeter of air (161). The regulations applied to metal and nonmetal mines and surface coal mines. There are no regulations however governing exposure to asbestos in underground coal mines. Finally, MSHA has regulated exposure to radon daughters and ionizing radiation (1969) and updated these standards once (1976) (see table 3-3).

Following a petition and a lawsuit filed by the Oil Chemical and Atomic Workers Union and the Health Research Group for a more stringent emergency temporary standard, and in response to a court order, MSHA has also proposed to revise the standards for radiation exposure to uranium miners (269). The proposed new standard is 4 working level months (WLM) which results in a cumulative lifetime exposure of 120 WLM over a 30-year period.[4] This standard is similar to the existing standard except that it also establishes a combined exposure limit for radon daughters, gamma radiation, and thoron daughters. Previously, thoron daughters were excluded from coverage altogether.

These standards merit special attention because uranium miners receive relatively high levels of radiation exposure compared to other nuclear workers and have high rates of occupational mortality (119). Radiation protection standards in general are based on the principle that exposures should be kept "As Low As Reasonably Achievable" (ALARA) (269). The proposed standard is consistent with the Federal Radiation Guidance, which is based on the recommendations of the International Commission of Radiological Protection (ICRP). A recent NIOSH evaluation however found a significant excess of lung cancer deaths from cumulative radon daughter exposures well below *100* WLM and concluded that a standard of 1 WLM a year is achievable (252). NIOSH is in the final stages of preparing a criteria document recommending a permissible exposure level.

Increased use of diesel engines in mines has raised concern about mine worker exposures to those fumes. Although MSHA routinely samples and regulates gaseous diesel emissions in accordance with the 1972 and 1973 TLVs, these are not based on carcinogenic effects. There is no standard regulating particulate diesel emissions except the limit on respirable dust, which also does not take into account carcinogenic effects. Finally, in 1986 OSHA revised its standard for asbestos. It is not clear whether MSHA will take additional action on regulating exposures to radiation, diesel fumes, or asbestos.

[4] A working level refers to a specified concentration of radon daughters in the air. A working level month is defined as the exposure to one working level for 170 hours. The commonly used dose-equivalent of 1 WLM is approximately 1 rem or 4.8 WLM = 5 rem (a rem is a measure of absorbed dose).

FDA REGULATORY ACTIONS

Carcinogens in foods and cosmetics are regulated by the Food and Drug Administration (FDA) under the FDCA. Of the regulatory statutes considered in this report, this act has by far the longest history. Its requirements have evolved over time. Prior to the 1950s, the statutory approach was to prohibit the sale of adulterated food. Food was considered adulterated if FDA could show

Table 3-3 .—MESA/MSHA Regulation of Carcinogens: Metal & Non-Metal Mines, Underground & Open Pit (other than coal), Sand, Gravel, and Crushed Stone Operations, Including Uranium Mine Radiation Standards

Substance	Adoption of 1973 ACGIH recommendations: NPRM	Final	Evidence	Revisions[a]: NPRM	Final	Basis
Asbestos	**8-29-73**	7-1-74[b]	Human	7-7-77	11-17-78	OSHA Standard
bis-(Chloromethyl) ether	**8-29-73**	7-l-74[b]	Human	7-7-77	11-17-78	OSHA Standard
Chromates	**8-29-73**	7-1-74[b]	Human	—	—	
Coal tar pitch volatiles	**8-29-73**	7-1-74[b]	Human	—	—	
Nickel carbonyl	**8-29-73**	7-1-74[b]	Human	—	—	
4-Aminobiphenyl (P-xenylamine)	**8-29-73**	7-1-74[c]	Human	7-7-77	11-17-78	OSHA Standard
Benzidine & Its salts	**8-29-73**	7-1-74[c]	Human	7-7-77	11-17-78	OSHA Standard
Beta -naphthylamine	**8-29-73**	7-1-74[c]	Human	7-7-77	11-17-78	OSHA Standard
4- Nitrodiphenyl	**8-29-73**	7-1-74[c]	Human	7-7-77	11-17-78	OSHA Standard
Beryllium	**8-29-73**	7-1-74[d]	Animal	—	—	
Chloromethyl methyl ether	**8-29-73**	7-1-74[d]	Animal	7-7-77	11-17-78	OSHA Standard
3,3' -Dichlorobenzidine	**8-29-73**	7-1-74°	Animal	7-7-77	11-17-78	OSHA Standard
Dimethyl sulfate	**8-29-73**	7-1-74°	Animal	—	—	—
Ethylenimine	**8-29-73**	7-1-74[d]	Animal	—	—	
44 -Methylene bis (2-chloraniline)	**8-29-73**	7-1-74[d]	Animal	7-7-77	11-17-78	OSHA Standard
N-Nitrosodimethylamine	**8-29-73**	7-1 -74"	Animal	7-7-77	11-17-78	OSHA Standard
beta-Propiolactone	**8-29-73**	7-1 -74*	Animal	7-7-77	11-17-78	OSHA Standard
2-Acetylaminofluorene	—	—	—	7-7-77	11-17-78	OSHA Standard
Carbon tetrachloride	—	—	—	7-7-77	11-17-78	P
4- Dimethylaminoazobenzene	—	—		7-7-77	11-17-78	OSHA Standard
Alpha-naphthylamine		—		7-7-77	11-17-78	OSHA Standard
Phenol	.	—		7-7-77	11-17-78	

Uranium mining radiation exposure standards:

Type of radiation	NPRM	Final	Basis	Court challenge/ petitions
Radon daughters	1-16-69[g]	2-25-70	FRC Guidance, 1967	
	6-24-70	12-8-70	–	
	9-25-75	6-10-76	EPA Guidance 5-25-71 (dewed from FRC recommendation 1 -15-69)h	
Gamma radiation	1-28-77	6-8-77	NCRP/ICRP recommendations	
Radon & thoron daughters and gamma radiation[i]	12-19-86	—	ICRP 26	4-21-80, Petition (OCAW /HRG) for 1 7 WLM/yr ETS 3-13-84 ***OCAW & Public Clitizen HRG v David Zeeger, 768*** F 2d 1480, (D C. Cir 8-2-85): 1-29-85 denied ETS. issued ANPRM

[a] In the revised regulations except for asbestos for which the exposure limit was reduced, MSHA restricted the use of the listed substances [o approved laboratory conditions by competent personnel The list was based on technica and medical evidence compiled by OSHA for the regulation of certain carcinogens According to MSHA however most If not al of the listed chemicals are seldom if ever used in the mineral industries subject to the Metal and Nonmetal Mine Safety Act

[b] Regulation consists Of ACGIH TLV

[c] ACGIH did not Issue a TLV regulation adopts ACGIH recommendation that no exposure or contact be permitted

[d] ACGIH did not issue, TLV regulat on adopts ACGIH *recommendation* that exposure should *be reduced* 10 a minimum

[e] Carbon tetrachloride was included on [he list of restricted chemicals even though it was not regulated as a carcinogen by OSHA It had already been promulgated as a mandatory standard by MSHA according to Information provided in response to the OTA request (Agenda to 9th Annual Meeting) but there is no indication whether this occurred

[f] Phenol was listed for acute toxicity and because it is a suspect carcinogen according to NIOSH even though it was not regulated by OSHA

[g] Prior to the 1970 final standards health and safety in uranium mines was regulated by the States Several Federal agencies provided advice and assistance and formed an interagency committee but held that the, lacked the proper statutory authority 10 regulate radiation exposure in privately owned uranium mines. In 1 (1',1-1 the U S Public Health Service began 10 investigate the levels of radiation exposure and the health effects of uranium mining al the request of the Colorado health department In "959 the Atomic Energy Commission did begin to respect mines and mills on Federal lands and required lessors to r ompliance with the 1957 radiation standards By doing so the AEC demonstrated the feasibility of controlling radiation levels in mines which prompted the interagency committee to or. ene a conference of governors from uranium mining States and representatives of the concerned Federal agencies on Dec .2 1960 It was at this meeting that the USPHS reported *preliminary data showing that uranium miners* had a lung cancer rate 5 times higher than the U S while male population

[h] The 1967 FRC (Federal Radiation Counc recommendations were based on the recommendations of the NCRP (National Commission on Radiological Protection) The revised 1969 FRC recommendations were based on a NAS report prepared for The Interagency Uranium Mining Radiation Review Group (IUMRRG) entitled Epidemiologic Studies of Uranium Miners which recognized an increased Incidence of lung cancer at 120 3[?] cum MI, e WL M

[i] The existing radiation exposure standards cover only radon daughters and gamma radiation in underground mines The NPRM for new standards also includes thoron daughters

SOURCES MSHA response 10 OTA request including *Federal Register* notices and agenda for the 19th Meeting of the Federal Metal & NonMetal Mine Safety Advisory Committee June 29 30 and July 1 1976 MSHA Ionizing Radiation Standards for Metal & NonMetal Mines -- Preproposal Draft November 1985 Comments on MSHA Preproposal Draft submitted by Public Citizen Health Research Group (HRG and the Oil Chemical and Atomic Workers International Union (OCAW) Feb 18 1986 Southwest Research & Information *Center NIOSH* Evaluation of Epidemiologic Studies Examining the Lung Cancer Mortality of Underground Miners prepared for MSHA 5-9-86 George T Mazuzan and J Samuel Walker Control of the Atom University of California Press 1984

that it was "ordinarily injurious to health" or that it contained an added substance that "may render it injurious to health" (section 402(a)(l)).

Starting in 1954, Congress enacted special statutory provisions for particular groups of substances that might be added to foods or cosmetics, first, pesticide residues (in 1954, now regulated by EPA), then food additives (1958), color additives (1960), and animal drug residues (1962).

A "food additive" is any substance, the intended use of which leads it to become a component of food either directly or indirectly. The 1958 Food Additives Amendment established a premarket approval process for food additives, although excluded from this are substances "generally recognized as safe" (GRAS) and substances that had received Federal sanction prior to 1958 ("prior sanction" substances). Food additives include substances used to alter the taste or composition of food, and packaging materials that may migrate into the food.

To approve a food additive, FDA must be convinced of the safety of the additive. On this point, the well-known "Delaney clause" provides "that no additive shall be deemed to be safe if it is found to induce cancer when ingested by man or animal, or if it is found, after tests which are appropriate for the evaluation of the safety of food additives, to induce cancer in man or animal."

For "unavoidable contaminants" found in food (such as aflatoxins in peanuts, mercury in fish, and PCBs in milk and fish), the FDA may set tolerance levels through formal rulemaking procedures. Alternatively, FDA has used more informal "action levels, " which are established without going through rulemaking. Because they are not regulations, action levels are easier to change than tolerances. Action levels and tolerances are both levels of a contaminant which, if exceeded, would render the food "adulterated" and lead FDA to bring court action to seize the foods

FDA's regulation of carcinogens was affected by an important case, *Monsanto v. Kennedy (129), which involved* a plastic bottle that FDA believed might release a suspected carcinogen into its contents and thus present a risk to consumers. The court ruled that FDA need not determine that a substance was a food additive based on a theoretical prediction of migration, although this is permissible if there is a safety concern. The court then went on to declare that FDA could exempt small amounts of substances in "de minimis situations" that "clearly present no public health or safety concerns. " A 1984 court decision, *Scott v. FDA (184),* specifically supported FDA's decision to allow the use of color additives that contain carcinogenic impurities, when FDA believes such use represents an insignificant risk. As discussed below, FDA has started to apply this by approving certain color additives even though they contain known carcinogens, arguing that the risks are insignificant.

As a result, FDA's carcinogen regulation has changed. Prior to 1982, food and color additives that contained carcinogenic impurities (formerly called "constituents") were banned, but since then the policy for such impurities is that, if a food or color additive itself does not cause cancer, but an impurity of the additive is a known carcinogen, the agency will use risk assessment to determine whether "under the general safety clause, there is a reasonable certainty that no harm will result from the proposed use of the additive" (245).

Role of Quantitative Risk Assessment

Over time, FDA has given quantitative risk assessment more importance. The first uses of quantitative risk assessment were for carcinogenic chemicals not subject to the Delaney clause. In 1973, FDA proposed to use risk assessment to specify the sensitivity of the analytic method used to determine the level of potentially carcinogenic animal drug residues (see ch. 2). The next application was for setting tolerances and action levels on food containing unavoidable environmental carcinogenic contaminants. The first uses of risk assessment for such contaminants appear to have been for aflatoxins in 1978 and PCBS in 1979 (table 3-4). In 1982, it was applied to carcinogenic impurities in color additives, which were not regarded as subject to the Delaney clause under FDA's impurities policy. Finally, risk assessment

'The authority to establish tolerance levels for pesticide residues on raw agricultural products was transferred to EPA in 1970 and will be discussed under the regulation of pesticides.

Table 3-4.—FDA: Carcinogens Associated With Foods and Cosmetics

Substance	When identified	Type of evidence	Petition	'NPRM	Final	Type of action/co=ment~
Acrylonitrile–as contaminant of acrylonitrile/styrene copolymer resin in the manufacture of beverage bottles	6-22-80, 11-24-81 risk assessment	Human, respiratory only animal, 1 species–rats	3-483 (Monsanto) requesting rule for safe use	NA	9-19-84	The agency had revoked all beverage container uses of acrylonitrile polymers 9-23-77 Action in 1984 allows its use based on new agency policy and development of a bottle with lower contaminant levels[a]
Aflatoxin	1-19-78, risk assessment	Human, animal		12-6-74, proposed tolerance 15 ppb in peanut products, 3-3-78, reopened comment period	–	In 1965 aflatoxin contaminated foods were declared adulterated at the detection limiat of 30 ppb In 1969 the level changed to 20 ppb which remains as the current action level[b]
2-Aninoanthraquinone	2-21-80	—	—	—	—	Hypothesized Impurity in several color addiatives; not found
4-Aminoazobenzene –in FD&C Yellow No 5	12-20-83, risk assessment	Animal, 1 species-rats	3-27-65	—	9-4-85	FD&C Yellow No. 5 permanently listed for use in cosmetics and externally applied drugs; contains 4-aminoazbenzene impurity[a]
—in FD&C Yellow No. 6	—	—	11-20-68	—	11-19-86	Permanently listed Yellow No.6. contains 4-aminoazobenzene impurity[a]
4-Aminobiphenyl —in Ext. FD&C Yellow No. 1	1954 evidence cited	Human, animal, 1 species–dogs	11-23-76, received comments about substance as contaminant of azo dyes	9-23-76	12-13-77	Terminated provisional listing of color additive for use in externally applied drugs and cosmetics because of possible benzidine impurity and 4-aminobiphenyl impurity
—in FD&C Yellow No. 5	12-20-83, risk assessment	—	3-27-65	—	9-4-85	Permanently listed Yellow No. 5 for use in cosmetics and externally applied drugs; contains 4-aminobiphenyl impurity[a]
	12-20-83, risk assessment	—	—	9-4-85	7-7-86	Adopted uniform specifications, including specifications on Impurities for all uses of Yellow No. 5
–in FD&C Yellow No. 6	—	—	11-20-68	—	11-19-86	Permanently listed Yellow No. 6; contains 4-aminobiphenyl impurity[a]
4-Amino-2-nltrophenol	4-29-80	—	—	—	—	Coal tar hair dye ingredient
2-Amino-5-nhro-thlazole	1-8-79	Animal, 1 species–rats	–		—	Metabolize of animal drug; manufacturer withdrew drug from market after notified about carinogenic metabolite by FDA

[a]The rules for safe use are based on a 1984 court decision that allowed safe exposure levels to be established for non carcinogenic additives I hat CO ntain carcinogenic impurities If the additive itself IS not shown to be carcinogenic (*Scott v FDA* 728 F 2d 322 (6th Cir 1984) See discussion In text

[b]Action levels are not required 10 be published for comment before they are established

'Coal tar hair dyes are exempt from the adulteration and color additive provisions found in sections 601 & 706 of the FDCA (21 U S C 361 376) provided the label bears a caution statement & patch test instructions to determine if the product causes skin irritation (*Fed Reg* 43 1101 1978)

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Table 3-4.—FDA: Carcinogens Associated With Foods and Cosmetics—Continued

Substance	When identified	Type of evidence	Petition	NPRM	Final	Type of action/comments
Aniline						
—in FD&C Yellow No. 5	4-6-79; 12-20-83, risk assessment	Animal, 1 species—rats	3-7-65	—	9-4-85	Permanently listed Yellow No. 5 for use in cosmetics and externally applied drugs; contains aniline impurity[a]
—in FD&C Yellow No. 6	—	—	11-20-68	—	11-19-86	Permanently listed Yellow No. 6; contains aniline impurity[a]
Asbestos—in talc	6-6-85, risk assessment	—	—		—	Cosmetic use of talc; risk assessment indicated lifetime risk is less than 1 in 1 million
Azobenzene						
—in FD&C Yellow No. 5	12-20-83, risk assessment	Animal, species—rats	3-27 65	—	9-4-85	FD&C Yellow No. 5 permanently listed for use in cosmetics and externally applied drugs; contains azobenzene impurity[a]
			—	9-4-85	7-7-86	Adopted uniform specifications, including specifications on impurities for all uses of Yellow No. 5
—in FD&C Yellow No. 6	—	—	-20-68	—	11-19-86	Permanently listed Yellow No. 6; contains azobenzene impurity[a]
Benzidine						
—in Ext. D&C Yellow No.	Cites 1973 studies	Human; animal, 4 species—dogs, rats, mice, hamsters	1-23-76, received comments about substance as contaminant of azo dyes	9-23-76	12-13-77	Terminated provisional listing of color additive for use in externally applied drugs and cosmetics because of possible benzidine impurity and 4-aminobiphenyl impurity
—in FD&C Yellow No. 5	12-20-83, risk assessment	Human; animal, 4 species—dogs, rats, mice, hamsters	3-27-65	—	9-4-85	Permanently listed Yellow No. 5 for use in cosmetics and externally applied drugs; contains benzidine impurity[a]
—in FD&C Yellow No. 5	12-20-83, risk assessment	Human; animal, 4 species—dogs, rats, mice, hamsters	—	9-4-85	7-7-86	Adopted uniform specifications, including specifications on impurities, for all uses of Yellow No. 5
Chloroform (Trichloromethane)	3-1-76, received NCI report	Animal, 2 species	12-30-75 (HRG)	4-9-76	6-29-76	Prohibited in human drugs & cosmetics; proposal to prohibit use in food contact articles
4-Chloro-	7-10-79	—	—	—	—	Coal tar hair dye ingredient[c]
4-Chloro-o-phenylene-diamine	6-10-80	—	—	—	—	Coal tar hair dye ingredient[c]
5-Chloro-	5-27-80	—	—	—	—	Hypothesized color additive impurity; not found
Cinnamyl anthranilate	6-19-80; 6-21-81 risk assessment	Animal, species—mice	—	5-25-82	10-23-85	Prohibited for use in food
C.I. Vat Yellow No. 4—in C.I. Vat Orange No. 1	7-20-83, risk assessment	Animal, species—mice	6-17-83 (Custom Tint Laboratories)	—	5-16-85	Listed C.I. Vat Orange No. 1 for coloring contact lenses; contains C.I. Vat Yellow No. 4 impurity[a]

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Table 3-4.—FDA: Carcinogens Associated With Foods and Cosmetics—Continued

Substance	When Identified	Type of evidence	Petition	NPRM	Final	Type of action/comments
p-Cresidine	4-29-80	—	—	—	—	Hypothesized Impurity m FD&C Red No 40
Dapsone (4,4'-Diaminodiphenyl-sulfone)	3-25-80	—	—	—	—	Hypothesized Impurity m FD&C Yellow Nos. 5 & 6; not found
D&C Orange no 17	1-20-83	Animal, 2 species–mice, rats	4-16-69	—	4-1-83	Provisional listing expired for use m ingested drugs and cosmetics
	—	—	—	—	8-7-86	Permanently listed for use m externally applied drugs and cosmetics
	—	—	—	—	10-6-86	Response to objections
	—	—	—	—	2-19-87	Clarification to preamble
D&C Red Nos. 19 & 37	8-12-82	Animal, 2 species–rats, mice	4-14-69	—	2-4-83	Terminated provisional listlng for ingested uses
	—		—		8-6-86	Terminated provisional listing for D&C Red No, 37
	—	—	—	—	8-7-86	Permanently listed D&C Red No 19 for use in externally applied drugs and cosmetics
	—	—	—	—	10-6-86	Response to objections
	—	—	—	—	2-19-87	Clarification to preamble
D&C Red Nos. 8 & 9	8-26-82	Animal, 1 species–rats	5-17-65	—	12-5436	**Permanently listed for use in ingested** drug and cosmetic lip products in limited amounts and in externally applied drugs and cosmetics
2,4-Diaminoanisole & 2,4-Diaminoanisole sulfate–as Ingredients in coal tar hair dyes	10-18-77, NCI study sent to FDA; 9-7-78, risk assessment	Animal, 2 species–rats, mice	10-19-77 (EDF); 12-14-77 (GAO recommendation)	1-6-78	10-16-79	Product warning statements required in absence of statutory authority to ban(2); 9-18-80, stayed by consent order, U.S. Dist. Ct. for the Southern Dist. of Georgia (Civil Action No. CV 480-71) and remanded to FDA for reconsideration & further rulemaking
2,4- Diaminotoluene	9-20-79; 6-30-83, risk assessment	–	—	—	1- 5-80	Denied use of adhesive in which this impurity formed
Dibutyltin diacetate–as contaminant of 2.2-oxamidobis(ethyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl) propionate)	10-18-79; 5-23-83, risk assessment	Animal, 1 species–mice	–	—	8- 9-83, 4-2-84, supplement to final rule	Rule for safe use of non-carcinogenic food packaging additive that may contain dibutyltin diacetate. [a]The supplement discloses the identity of the carcinogenic constituent which previously was withheld as a trade secret
	—	—	—	—	12-4-85	Request for hearing was denied
D1-(2-ethylhexyl) adipate	11-12-80, 7-21-81, risk assessment	Animal, 2 species–rats, mice	–	—	—	Under study –indirect mechanism of action suspected

[a]The rules for safe use are based on a 1984 court decision that allowed Safe exposure levels to be established for non-carcinogenic additives that contain carcinogenic impurities If the additive itself is not shown to be carcinogenic (*Scott v FDA* 728 F 2d 322 **(6th** Cir 1984)) See discussion in text

[c]Coal tar hair dyes are exempt from the adulteration and color additive provisions found in sections 601 & 706 of the FOCA (21 U S C 361 376) provided the label bears a caution statement & patch test instructions to determine if the product causes skm irritation ***(Fed Reg*** 43 1101 1978)

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Table 3-4.—FDA: Carcinogens Associated With Foods and Cosmetics—Continued

Substance	When Identified	Type of evidence	Petition	NPRM	Final	Type of action/comments
D1-(2-ethylhexyl) phthalate	11-12-80, 7-21-81, risk assessment	Animal, 2 species–rats, mice	—	—	—	Under study, indirect mechanism of action suspected
1,4-Dioxane–as impurity m 10 food contact additives & 1 saniatizing solution used on food contact surfaces[d]	8-21-79; 11-19-81, risk assessment	Animal, 1 species–rats	3-19-82, 4-22-83, 6-14-84, 2-3-81, 4-20-84, 2-25-85, 12-28-79, 6-3-83, 9-8-83, 9-3-82, 3-5-86	–	9-28-83, 9-10-85, 8-13-86, 9-5-86, 9-19-86, 9-24-86, 9-24-86, 9-24-86, 12-31-86, 1-6-87, 1-7-87	Rules for safe use of food-contact additives that contain 1,4-Dioxane
1,3-Dlphenyltrlazene						
—in FD&C Yellow No 5	12-20-83, risk assessment	Animal, 1 species–mice	3-27-65	—	9-4-85	FD&C Yellow No.5 permanently listed for use m cosmetics and externally applied drugs; contains 1,3-diphenyltriazene impurity[a]
			—	—	9-4-85	Adopted uniform specifications including specifications on impurties, for all uses of FD&C Yellow No. 5
—in FD&C Yellow No 6		—	11-20-68	—	11-19-86	Permanently listed Yellow No. 6; contains 1,3-diphenyltriazene impuriy[a]
Dulcin (sucrol), (4-ethoxy-phenylurea)	no date	Chrome toxicity data in rats	—	—	1-19-50	Banned as food additive
Epichlorohydrin-contained in polyamide-epichlorohydrin water-soluble thermosetting resins (retention aid in paper coating)	11-29-82, risk assessment	—	4-9-82 (Sandox Colors & Chemicals)	—	8-19-83	Amended regulations to remove upper viscosity limit of the retention aid–(used m paper coating as indirect food additive); contains epichlorohydrin impurity[a]
		—	—	—	4-24-84	Clarification of final rule
	—	—	—	—	12-4-85	Denied request for hearing
17-b-Estradiol	*11-14-79, 5-23-83,* risk assessment	—	—	—	4-9-84	Animal drug, hormone naturally occurring in animals
Ethylene oxide–as Impurity m 9 food contact additives[e]	1-5-82; 4-7-86, risk assessment	—	6-14-84, 2-3-81, 4-20-84, 2-25-85, 12-28-79, 6-3-83, 9-8-83, 9-3-82, 3-5-86	—	8-13-85, 9-5-86, 9-19-86, 9-24-86: 9-24-86, 9-24-86, 9-24-86, 12-31-86, 1-6-87, 1-7-87	Rules for safe use of several food contact additives that may contain ethylene oxide impurity[a]
Ethylene thiourea (Impurity in mercaptomidazoline)	No date	''Known carcinogen'	—	*4-24-73*	11-30-73	Banned mercaptolmldazohne and 2-mercaptiomidazoline m food contact articles due to possible Impurity
Flectol H (1.2-dihydro-2.2,4 -tri-methylquinoline, polymerized)	No date	Animal. 1 species	—	—	4-7-67	Banned m food contact articles
Hydrazine	6-12-79, (cities IARC), 6-8-82, risk assessment	Animal, 2 species–mice, rats	—	6-12-79	—	To prohibit food additive use, permitted as a boiler water additive with limitation of zero in steam contacting food
Lactitol	5-2-85	—	5-19-83		—	Not permitted as a food ingredient; petition requests food addiative regulation

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Table 3-4.—FDA: Carcinogens Associated With Foods and Cosmetics—Continued

Substance	When identified	Type of evidence	Petition	NPRM	Final	Type of action/comments
Lactose	5-2-85			—	—	Natural component of food including milk, FASEB report (9-86) states that lactose is not significantly tumorigenic in humans, believes it is necessary to repeat animal study
Lead acetate	3-6-79, found to be absorbed by skin. 5-6-80, 5-23-80, risk assessment	Animal, 2 species–rats, mice (by ingestion)	6-29-73 (Comm of Progressive Hair Dye Industry) requesting permanent listing[f]	12-10-63	0-31-80, 3-6-81, response to objections & removal of stay	Permanently listed for use as color additive in hair dyes
4.4'-Methylenebis (2-Chloroaniline)	**No date**	**Animal, 1 species**	–	—	2-2-69	Banned in food contact articles
Methylene chloride	1-20-83, 4-23-85, risk assessment	Animal, 1 species–mice (suggestive m rats)	–	12-18-85	–	Proposed to ban in cosmetics but not in decaffeinated coffee because risk was determined negligible
4,4' -Methylene dianiline	4-7-83, 5-16-83, risk assessment	–	—		—	
b-Naphthylamine						
—in FD&C Yellow Nos. 3 & 4	No date	No carcinogenic evidence cited	(Dye Stuffs & Chemicals) –		10-12-60	Denied petition of Dye Stuffs & Chemicals to restore color additives to provisional list with 25 ppm tolerance in food, possible impurity m these color additives
–in FD&C Yellow Nos. 3 & 4	Cites 1974 IARC report	Human, animal, 4 species—mouse, hamster, dog, monkey	–	—	10-12-60	Provisional listing of these color additives terminated because b-naphthylamine is possible impurity
—in Red Nos. 10, 11, 12, & 13	Cites 1974 IARC report	Human, animal	8-6-73 (for permanent listing), withdrawn 10-21-77	9-23-76	12-13-77	Prohibited these color additives from use in drugs & cosmetics because b-naphthylamine is a possible Impurity; terminated provisional listing
—in Orange-B	1-19-78, identified as contaminant of Orange-B	Human, animal	—	10-3-78	—	To revoke listing of Orange-B for use m food; not certified for use m food since 10-78
Nitrilo triacetic acid	10-18-79	—	—	—	—	—
N-Nitrosodimethylamine						
—as contaminant m malt beverages	1956	Animal, more than 2 species–rats, mice, others	–	—	10-25-79, action level announced in press release[b]: notice of comphance guide published 6-10-80	Action level established at lowest level at which presence can be confirmed in malt beverages

[a]The rules for safe use are based On a 1984 court decision that allowed safe exposure levels to be established for non carcinogenic additives that contain carcinogenic impurities if the additive itself is not shown to be carcinogenic (*Scott* v *FDA* 728 F 2d 322 (6th Cir 1984)) See discussion in text

[b]Action levels are not required to be published for comment before they are established

[d]Food contact additives which Contain 14. Dioxane for which safe use rules were issued ethylene oxide adduct of 2479 tetramethyl-5-decyn-47-diol polyoxyethylated (5 moles) tallow amine and alpha alkyl-omega-hydroxy poly (oxyethylene) ethoxylated octadecylamine reacted with octadecanoic acid *alpha* sulfo *omega* (dodecyloxy) poly (oxyethylene) ammonium salt impact modified Nylon MXD-6 sulfosuccinic acid 4-ester with polyethylene glycol nonylphenyl ether disodium salt *alpha*-alkyl (C10-C14) omega- hydroxypoly (oxyethylene) poly (oxypropylene) and *alpha* alkyl (C 12 **C** 18)-*omega* hydroxy-poly (oxyethylene) poly (oxypropylene) polyoxyethylene cetyl alcohols and polyoxyethylene oleyl ether *alpha*-(p-nonylphenyl)-*omega*-hydroxy polyloxyethylene) and diethyleneglycol dibenzoate Sanitizing solution used on food contact surfaces *alpha*-alkyl (C 11 Cl 5) omega hydroxypoly (oxy theylene) and *alpha* (p nonylphenyl) ***omega*** hydroxypoly (oxy ethylene)

[e]Food contact additives Which may contain ethylene oxide for Which Safe use rules were issued ethoxylated octadecylamine reacted with octadecanoic acid *alpha* sulfo *omega* (dodecyloxy) poly (oxyethylene) ammonium salt impact modified Nylon MXD-6 sulfosuccinic acid 4-ester with polyethylene glycol nonylphenyl ether disodium salt *alpha* alkyl (C10-C14)-omega. hydroxypoly (oxyethylene) poly (oxypropylene) and *alpha* alkyl (C1 ?-C 18)-*omega* hydroxy-poly (oxyethylene) poly (oxypropylene) polyoxyethylene cetyl alcohols and polyoxyethylene oleyl ether *alpha*-(p nonylphenyl) *omega*-hydroxypolyloxyethylene) and diethyleneglycol dibenzoate

[f]The petition was filed in response f. 1 3,.73 notice (*Fed Reg* 382996 1973)1 hat metallic salts or vegetable colorants could no longer be marketed unless a petition was filed by 7-3073 In the NPRM manufacturers were advised that they Were not eligible for coal far hair dye exemptions & dafa was requested to make final determination The closing date was postponed several times pending study Completions

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Table 3.4.—FDA: Carcinogens Associated With Foods and Cosmetics—Continued

Substance	When indentified	Type of evidence	Petition	NPRM	Final	Type of action/comments
—as contaminant m 5-chloro-2-methyl-4 isothiazolin-3 -one & 2-methyl-4-isothiazolin-3-one	—	—	1-19-80, 2-22-80 to establish rule for safe use	–	2-1-85	Rule established for safe use of additive containing DMNA impurity in adhesives and paper coating which contact food[a]
5-Nitro-o-toluidine	3-4-80	—	—	—	—	Hypothesized impurity in several color additives; not found
2-Nitro-p-phenylenediamine	11-27-79		—	—	—	Coal tar hair dye ingredient
2-Nitropropane	4-25-77 NIOSH Bulletin, 4-7-86, risk assessment	Animal, 2 species–rats, rabbits	–	12-1-78	—	To prohibit m food packaging adhesives
N-Nitrosamines–as contaminants in rubber baby bottle nipples	1981, found as a problem m rubber baby bottle nipples	—	—	—	12-27-83, action level announced; revised 6-26-84	Action level established at lowest avoidable level (10 ppb m any specific N-nitrosamine)
011 of Calamus	No date	Animal, 1 species	–	—	5-9-68	Banned use of calamus and its derivatives m food
PCB'S (Arochlor)	9-23-80	—	—	3-18-72 (& others)	7-6-73 (& others)	Tolerances estalished to limit exposure
P-4,000 (1-n-propoxy-2-amino-4-nitrobenzene)	No date	Chrome toxicity data m rats	–	—	1-19-50	Banned as food additive
o-Phenylphenol	5-31-84	—	—	—	—	—
Polynuclear Aromatic Hydrocarbons (PAH) —in carbon black	ACS Monograph #173	Certrain PAHs are known carcinogens	7-24-73	—	9-23-76	Petition denied and provisional listing terminated for use of carbon black as color additive because PAH possible impurity
—in graphite	—	—	8-6-73	—	11-29-77	Provisional listing terminated for use of graphite in externally applied cosmetics because contains PAH Impurities
Radioactive Contamination of Food (accidental)	—	Based on guidance issued by Federal Radiation Council, 7-64, 5-65	–	12-15-78 (proposed "Protective Action Guidelines" for State and local agencies)	*10-22-82,* prop recommendations withdrawn, issued notice of recommendations (not codified)	Recommended protective action at 0.5 rem whole body, 1.5 rem thyroid; emergency protective action (when there is high dietary & social cost or impact) at 5 rem whole body, 15 rem thyroid
Saccharin	—	Animal, 1 species–rats	–	4-15-77	Withdrawn	Proposal to revoke as ingredient in food was withdrawn because of congressional action
Safrole & Isosafrole	6-16-78	Long term studies	–	—	12-3-60	Banned addition of safrole, oil of sassafras and related substances to foods; some GRAS substances may contain miniscule amounts of safrole. Cosmetics: low priority for further evaluation because low potency carcinogen with limited exposure

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Table 3-4.—FDA: Carcinogens Associated With Foods and Cosmetics—Continued

Substance	When identifed	Type of evidence	Petition	NPRM	Final	Type of a acation/comments
2,3,7,8-Tetrachlorodienzo-p-dioxin (TCDD)	1026-78 risk assessment	–	–		–	Unavoidable contaminant. advisory issued to Great Lakes States on TCDD in fish in 1981
Tetrachloroethylene	5-13-80	Animal, 1 species–mice	–	–	–	–
Thiourea	6-16-78		–			Possible cosmetic ingredient, no longer used in cosmetics to FDA's knowledge
o-Toluidine	4-1-80		–	–	–	**Impurity in several color additives found along with p-toluidine, but at lower levels, p-toluidne Specification also limits o-toluidine**
p-Toluidine						
–as contaminant of D&C Green No 6	2-24-81, 2-24-81, risk assessment	Animal, 1 species–mice	–	3-21-86	10-27-86	Adopted uniform specifications, including specification on p-toluidine impurity, for all suture uses of D&C Green No. 6
	–	–	11-20-68	·	4-2-82	Permanently listed D&C Green No, 6 for use in externally applied drugs & cosmetics; contains p-toluidine impurity[a]
	–	–	1-14-83, 1-28-83 (3 petltlons)	–	3-29-83	Listed D&C Green No. 6 for use in contact lenses
	–	–	2-14-85, 3-29-83	–	3-21-86	Provided for additional uses of D&C Green No. 6 for coloring absorbable sutures
	–	–	–	3-21-86	10-27-86	Adopt uniform specifications, including specification on p-toluidine impurity, for all suture uses of D&C Green No 6
–as contaminant of D&C Green No. 5	–	–	11-20-68	–	6-4-82, 11-2-82, stay removed	Permanently listed D&C Green No, 5 for use in drugs and cosmetics, contains p-toluidine impurity[a]
–as contaminant of D&C Red Nos. 6 & 7	–	–	8-6-73	–	12-28-82; 7-29-83, stay removed	Permanently listed D&C Red Nos. 6 & 7 for use in drugs & cosmetics, contains p-Toluidine impurity[a]
1, 1,2-Trichloroethane	11-20-79	Animal, 1 species–mice	–	–	–	Permitted for use in food packaging adhesives
1, 1,2-Trlchloroethylene	3-21-75 NCI report	Animal, 1 species–mice	6-24-75 (HRG)	*9-27-77*	–	Agency Information indicates coffee decaffeination and cosmetic uses discontinued

[a]The rules for safe use are based on a 1984 court decision that allowed safe exposure levels 10 be established for non carcinogenic additives that contain carcinogenic impurities If the additive itself is not shown to he carcinogenic *Scott . FDA* 728 F 2d 322 (6th Cir 1984)) See discussion in text

[c]Coal tar hair dyes are exempt from the ad ulteration and color additive provisions f.. nd in sections 601 & 706 of the FDCA(21 USC36' 3715) provided the label bears a caution statement & patch test instructions to determine if the product causes skin irritation(*Fed Reg* 43 1101 1978)

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Substance	When identified	Type of evidence	Petition	NPRM	Final	Type of action/comments
Trimethylphosphate	Includes risk assessment	Animal, 2 species–rats, mice	1-28-80 (Sunkyong Fibers)	–	—	Petition for use of trimethylphosphate in manufacture of polyethylene phthalate polymers; withdrawn 4-4-80; impurity in pesticide used in animal feed
Urethane						
—impurity in diethylpyrocarbonate	No date	Not regarded as safe, no evidence cited[g]	—	2-11-72	8-2-72	Banned diethylpyrocarbonate because urethane is possible impurity
—in alcoholic beverages	—		11-24-86	—		CSPI is requesting recall of alcoholic beverages adulterated with high levels of urethane
Vinyl chloride (impurity in vinyl chloride polymers)	1-4-73, identified in alcoholic beverages stored in vinyl chloride polymer containers		—	5-17-73	Withdrawn 9-3-75	Re: restriction from use of vinyl chloride polymers in alcoholic beverage containers
	1974	Human	—	4-2-74	8-26-74	Prohibited use of vinyl chloride as ingredient of drug & cosmetic aerosol products, NDA required for use in drugs
	—	Animal	—	9-3-75	Withdrawn 2-3-86	Re: restriction on use of vinyl chloride polymers in contact with food
	Cites 1979 IARC Monographs; 5-27-82 (risk assessment)	Animals, 3 species–mice, rats, hamsters	—	2-3-86	Pending	Rule for safe use of vinyl chloride potymers based on new technical capability to reduce levels of vinyl chloride monomer in vinyl chloride polymer resin and on new interpretation of legal requirements

[a]The rules for safe use are based on a 1984 court decision that allowed safe exposure levels to be established for non-carcinogenic additives that contain carcinogenic impurities If the additive itself IS nOt shown to be carcinogenic (*Scott* V *FDA* 728 F 2d 322 (6th Cir 1984)) See discussion m text

gNo carcinogenic evidence is cited by the FDA for this action However it is listed as a carcinogenic substance in the NTP *Annual Report*

was extended to substances covered by the Delaney clause, under a de minimis interpretation of that clause. In 1985, FDA proposed to allow the continued use of methylene chloride as a direct food additive based on the results of a risk assessment. In 1986, some carcinogenic color additives were permanently listed based on the results of risk assessments (see below).

Regulatory Actions on Carcinogens in Foods and Cosmetics

FDA actions concerning carcinogens in foods and cosmetics can be grouped based on the type of material and the kind of FDA action. The types of materials are direct food additives, indirect food additives (generally from packaging materials and food-processing equipment), color additives (both for ingestion and for external use only), contaminants or potential contaminants of food or color additives, unavoidable environmental contaminants in foods, and cosmetic ingredients. FDA actions may include banning the substance (or terminating a provisional listing), setting a rule for safe use of an additive, requiring warning labels, and setting tolerances and action levels.

Prior to 1958, the FDA had prohibited the food additive use of two carcinogens: Dulcin (4-ethoxyphenylurea) and P-4000 (1-n-propoxy-2-amino-4-nitrobenzene), both in 1950 (see table 3-4). Since then, FDA has banned four direct food additives: safrole (1960); oil of calamus (1968); diethylpyrocarbonate (DEPC) (1972), which forms the carcinogen urethane);[b] and cinnamyl anthranilate (1985). FDA has also proposed to prohibit the use of hydrazine, trichloroethylene, and Saccharin as food additives. The proposal for Saccharin was issued in 1977 but was not made final because of congressional action mandating that Saccharin remain on the market. For hydrazine and trichloroethylene, no final action has been taken.

FDA is also proposing a rule to allow the continued use of methylene chloride to decaffeinate coffee (in contrast to banning its use in cosmetics). This use for decaffeination is being justified on the grounds that an assessment reveals that the risk from this use is de minimis.[7]

Indirect food additives are generally packaging materials in contact with food and processing equipment. FDA has banned outright two indirect food additives: flectol-H (1967) and MBOCA (1968). In the mid-1970s, FDA had also banned certain uses of bottles made from acrylonitrile copolymers and polyvinyl chloride because of concern that residual acrylonitrile and vinyl chloride might leach into the liquids contained in the bottles. In the 1980s, FDA issued a rule to allow acrylonitrile copolymer bottles and proposed to allow polyvinyl chloride bottles. FDA's argument is that new manufacturing technology can assure that leaching of the residual chemicals from these bottles will be minimal and that FDA has the authority to establish specifications for carcinogenic impurities in regulations for the safe use of additives. FDA has also issued a safe use rule for Epichlorohydrin (1983), dibutyltin diacetate (1983), 1,4-dioxane (1985), dimethylnitrosamine (1985), and ethylene oxide (1986), which are carcinogenic impurities of certain packaging materials. FDA has proposed, but not taken final action on, other indirect food additives in packaging materials: 2-nitropropane and chloroform.

Under the Color Additives Amendment of 1960, FDA established a provisional listing of color additives then in use with the aim of reviewing their suitability for permanent listing for use in foods, drugs, and cosmetics. The original amendments gave industry 2½ years (until the end of 1963) to demonstrate the safety of provisionally listed color additives. However, FDA has extended this deadline a number of times since then. Although the provisional color list was established shortly after enactment of the Color

[6] Urethane has been in the news lately because it is found as a by-product of fermentation in several types of wines and distilled spirits. FDA has been petitioned to take action on urethane levels.

[7] Two other well-publicized actions involved some concern for carcinogenicity, although FDA's final decisions were ultimately based on other grounds. In 1969 FDA removed cyclamates from its lists of GRAS substances. While initially there were concerns about a positive animal study, after review FDA concluded that cyclamates were not carcinogenic. But the listing termination was continued because it was not shown to be safe. In 1976, FDA removed FD&C Red No. 2 from its provision] list of color additives because FDA was not convinced of the safety of this additive. This decision was based partly on an inconclusive study on carcinogenicity. Furthermore, no studies were under way to provide the data necessary to establish safety. Because these chemicals were additives, the manufacturer has the burden of providing this evidence.

Additives Amendment in 1960, the process of obtaining the necessary toxicity data and making regulatory decisions has lasted until now.

Today, 25 years later, there are only a few substances left on this provisional list. For a given color additive, FDA regulatory actions described in table 3-4 include terminating the provisional listing of a color or placing it on the "permanent" list. The provisional list originally included over 200 color additives. As of 1985, from the original list, 126 have been permanently listed, 63 have been removed from the market, and 10 have remained on the "provisional" list (210).

FDA has terminated the provisional listing of several color additives, effectively banning them, because they were carcinogenic or potentially contaminated with a carcinogen. These include Ext. D&C Yellow Nos. 9 and 10; D&C Red Nos. 10, 11, 12, and 13; orange-B (which may contain beta-naphthylamine); Ext. D&C Yellow No. 1 (which may contain benzidine and 4-aminobiphenyl), and carbon black and graphite (containing polynuclear aromatic hydrocarbons). FDA permanently listed lead acetate as a color additive for use in hair dyes in 1980, arguing that the lead exposure was small compared to background exposure and that the estimated risk was insignificant.

Since 1982, following its "impurities policy" (described above), FDA has permanently listed several colors even though they contain known carcinogens. These include D&C Green Nos. 5 and 6, and D&C Red Nos. 6 and 7 (all containing p-toluidine), FD&C Yellow No. 5 (containing 4-aminoazobenzene, 4-aminobiphenyl, aniline, azobenzene, benzidine, and 1,3-diphenyltriazene), FD&C Yellow No. 6 (containing 4-aminoazobenzene, 4-aminobiphenyl, aniline, azobenzene, and 1,3-diphenyltriazene), and CI Vat Orange No. 1 (containing CI Vat Yellow No. *4* as a contaminant).

In 1986, FDA applied a de minimis policy to colors that themselves are carcinogenic in animal studies. D&C Red Nos. 8, 9, and 19, and D&C Orange No. 17 were identified by FDA as carcinogenic in 1982 and 1983. D&C Red No. 9, in fact, tested positive in a National Toxicology Program (NTP) bioassay. In theory, based on the traditional interpretation of FDCA, these carcinogenic color additives should be candidates for banning from drugs and cosmetics. In August and December 1986, FDA permanently listed these colors, arguing that the estimated risk was low. In a February 1987 *Federal Register* notice, FDA went on to argue that because the estimated risk in humans was low, the color additives in question were, for purposes of the Delaney clause, not animal carcinogens either, notwithstanding the bioassay results. In the August notices, FDA had stated that each of these colors (D&C Orange No. 17 and D&C Red No. 19) "induces" cancer in animals. In the new notice it explained:

> This statement reflected FDA's policy, as a matter of scientific analysis . . . that any chemical shown to induce cancer even in only one strain, gender, and species, at one dose in one experiment, is an animal carcinogen. This statement did not represent a conclusion that this substance induces cancer in animals within the meaning of [the Delaney clause]. . . .
>
> . . . a conclusion for purposes of the Delaney clause that a substance at a given level poses a de minimis risk to humans implicitly includes the conclusion that a de minimis level of risk at a comparable level of exposure is presented to animals. Accordingly, D&C Orange No. 17 [and D&C Red No. 19] can not be said to induce cancer in animals, as well as in man, within the meaning of the Delaney clause. When a substance causes only a de minimis level of risk in animals, it cannot be said to induce cancer in animals within the meaning of the Delaney clause [239,240].

FDA has also acted on certain other ingredients of cosmetics. It has banned vinyl chloride in aerosol products, prohibited chloroform in cosmetics, and proposed to ban methylene chloride from cosmetics. FDA also attempted in 1979 to require a label on coal tar dyes (which contain 2,4-diaminoanisole and its sulfate) warning of animal evidence for carcinogenicity. In 1980, a Georgia court, in a consent decree, remanded this regulation back to FDA for further consideration, including development of a risk assessment. No further action has occurred.

For potentially carcinogenic unavoidable environmental contaminants, FDA has set regulatory tolerance levels for fish contaminated with PCBS. FDA has also set the more informal action levels

for aflatoxins, dimethylnitrosamines (in malt beverages), and N-nitrosamines (in baby bottle nipples).

The direct food additives that FDA has banned are generally carcinogenic in a single species. For the color additives that FDA has banned, the carcinogenic substances at issue were beta-naphthylamine, benzidine, 4-aminobiphenyl, and polyaromatic hydrocarbons—all of which are known human carcinogens and carcinogenic in several animal species. For most other color additives and indirect additives for which safe use rules were issued, the original determination of potential carcinogenicity from impurities or substance migration was usually based on animal data, often in one species.

Table 3-4 also indicates a number of substances that FDA has identified as carcinogenic, but for which no final regulations have been issued. In FDA's view, most of these regulations were not needed because the hypothesized impurity was never actually found or the risk was determined to be insignificant. FDA still might take action on a case-by-case basis if a problem was discovered (182).

Regulation of Animal Drug Residues

Prior to 1962, animal drug residues in food were subject to the Delaney clause, but in 1962 Congress enacted the "DES (Diethylstilbestrol) Proviso," which permits the use of carcinogenic drugs in animals, providing that their residues could not be detected in edible portions of tissue or foods derived from living animals according to methods approved by FDA. (See chapter 2 for a discussion of the sensitivity of method for detecting such substances.)

FDA identified (in its response to OTA) 16 carcinogens that are or were administered as drugs to animals, or are potential drug contaminants, and that might leave residues in animal tissues to which people may be exposed. FDA banned the *use* of DES in animal drugs, denied approval of one substance (which was however overturned in court) (Gentian violet), and has proposed to withdraw seven other substances. FDA has required residue studies on six substances, including four that it has proposed to withdraw. Three of those four were instead regulated under FDA's policy for endogenous or naturally occurring hormones under which a certain amount of increase over the naturally occurring levels is permitted.[8] For two substances, residue studies are all that FDA has required. In the case of Reserpine, the sponsor withdrew the application for approval, while for three other animal drugs, no actions are expected (see table 3-5). For one substance, aniline hydrochloride, which is a contaminant of an animal drug, FDA required that it's levels be reduced.

The only animal drug successfully banned is DES, on which there is human evidence from human uses of this drug. The lack of action on potentially carcinogenic animal drugs has also been criticized by the House Committee on Government Operations. In particular, the committee indicated that even though FDA has determined several animal drugs were carcinogenic (dimetridazole, ipronidazole, and carbadox), FDA has not removed these drugs from the market nor has it required that adequate residue monitoring methods be developed. In addition, while FDA had never given premarket approval to Gentian violet and its seizure orders had been supported in a number of courts, FDA has temporarily stopped seizing products containing Gentian violet because one lay jury determined this use to be "generally regarded as safe." Later animal tests revealed Gentian violet to be an animal carcinogen. The Committee criticized FDA for failing to take some action based on this evidence (211).

Regulation of Carcinogenic Human Drugs

Human drugs are subject to premarketing approval based on risk-benefit criteria for the intended condition of use (233). When a drug has a significant effect on an incapacitating or fatal

[8]The hormone policy was announced in guidelines for toxicological testing published in conjunction with FDA's proposed sensitivity of method procedures (mentioned above). Under the hormone policy, FDA distinguishes between endogenous and synthetic hormones. Endogenous hormones are regulated based *on* the *increase* over endogenous levels of the hormone found in the residue studies. For synthetic hormones, a study is required to determine the hormone no-effect level. If they cause tumors only in the endocrine target organs, the safety standard is based on the no-effect level. Otherwise the standard is based on the carcinogenicity study (102).

Table 3-5.—Potentially Carcinogenic Animal Drugs Considered for Regulation by FDA[a]

Drug	When identified (type of evidence)	Petition	Proposal to withdraw	Final	Court action/challenae
Aniline hydrochloride	—	—	—	**Level of contaminant** reduced	—
Carbadox (& metabolites)	1978 (animal–rats, mice)	5-9-86	—	Required residue & metabolism studies	—
DES[b]	1964 (animal–mice), no date (human)	None	3-11-72 (premixes)	8-4-72, (premixes)	Reversed & reinstated, *Hess & Clark* v. *FDA, 161* U.S. App. D.C 395, 495 F.2d 975 (DC Cir 1974)
	—	—	1-12-76 (hearing granted 11 -26-76)	9-21-79	DES is no longer permitted for use m animal drugs, upheld Rhorre *Poulenc, Inc , Hess & Clark Division v FDA, 636* F.2d 750 (DC. Cir, 1980)
		—	6-21-72 (premixes & implants)	4-27-73 (Implants)	—
	—	—	3-27-74 (to revoke method of analysis)	—	*Chemetron Corp. v U S DHEW, 95* F.2d 995, 997 (0 C. Cw. 1974)
Dimetridazole	1971 (animal–rats)	5-9-86	12-17-86	—	—
3.5-Dinitrobenzamide	1970 (animal–rodent) [c]	—	—	Level of human exposure from use m animals to determine further testing for hazard	—
Estradiol benzoate	1974 (IARC, literature reviews re sex hormones)	None	-5-79 (9-22-72, requested more residue data)	Residue studies provided	Regulated under FDA hormone policy
Estradiol monopalmitate	1974 (IARC, literature reviews re sex hormones)	None	-5-79 (requested more residue data 9-22-72)	No residue studies provided	—
Furazolidone	1964 (animal–rats, mice tumorigenic evidence), 1974 (carcinogenic evidence)	None	-4-71, 5-13-76, 9-4-84		Administrative Law Judge initial decision recommends withdrawal of NADAs, 11-12-86

[a] **Other potentially carcinogenic animal drugs were mentioned in hearings on the "Regulation of Animal Drugs by the FDA" before the House Committee on Government Operations which were not mentioned in the information provided by the agency in response to the OTA request These include Albendazole which was found carcinogenic in rats and mice by the CVM Cancer Assessment Committee in a July 1984 meeting. In 1979 it had been regarded as a suspect carcinogen and was not approved except for emergency and investigational use It was ordered off the market in a letter dated Nov 8, 1984 (Hearings, p. 424). A proposal to withdraw dibutyltin dilaurate was issued Aug. 29, 1978 but, according to an agency memo, products that contain it are still marketed under other NDAs. Dibutyltin dilaurate is a suspect carcinogen because it is related to dibutyltin diacetate which is carcinogenic according to NTP results. (Hearings, p. 187; FDA memorandum "Re-evaluation of the Status of Certain Marketed Drugs.") The memo also mentions Ronnel which is potentially contaminated with dioxin which is carcinogenic in rats. According to the memo however, the agency did not have enough evidence to take regulatory action and recommended requesting more data on the level of dioxin contamination in Ronnel (Hearings, pp. 188-189).**

It was also noticed that iron dextran complex and several estrogens are regulated according to information in the *Annual Report on Carcinogens* but do not appear on the list provided by the FDA. It also appears from the hearing documents that several substances may have been regulated through informal procedures, such as Albendazole which was regulated by correspondence between the agency and the sponsor so the listing may not be complete

[b] **1962 Congress enacted the "DES Exception" to the Delaney Clause" permitting the use of carcinogenic drugs in animals providing that they could not be detected in edible portions of tissue or foods derived from living animals according to methods determined by the FDA In 1962, regulations were promulgated permitting the use of DES and establishing detection methods. In the early 1970s however, the USDA found residues at levels below the sensitivity of the prescribed method**

[c] **The drug is regulated as a Carcinogen under the "DES Exception., (see footnote b) Information about the Identification of the drug as a carcinogen and the type of evidence relied on was not provided**

continued on next page

Table 3-5.– Potentially Carcinogenic Animal Drugs Considered for Regulation by FDA[a]—Continued

Drug	When indentified (type of evidence)	Petition	Proposal to withdraw	Final	Court action/challenge
Gentian violet	1985 (preliminary animal evidence-mice) [c d]		Denied approval 3-3079	–	Overturned approved for use as mold inhibitor in poultry feed *Marshall Minerals v FDA 661* F.2d 409 (5th Cir. 1981)
Ipronidazole [e]	1978 (animal)	5-9-86	Proposal to withdraw recommended by CVM in 1984	–	
Melengestrol acetate	Animal [c]	–	–		–
Nitrofurazone	1964 (animal–rats mice tumongenic evidence), 1974 (carcinogenic evidence)	None	3-31.71 8-17-76 9.4-84	–	Same as furazolidone
Progesterone	[c]	–	1.5-79	Residue studies provided	Regulated under FDA's hormone policy
Reserpine	–		–	5-16-84	–
Testosterone propionate	[c]	–	1-5-79	Residue studies provided	Regulated under FDA's hormone policy
Zeranol	Animal'	–	–	Required residue studies and chronic bioassay	–

[a] Other potentially carcinogenic animal drugs were mentioned in hearings on the "Regulation of Animal **Drugs by-the FDA" before the House Committee on Government Operations which were not–mentioned** in the Information provided by the agency in response to the OTA request These include Albendazole which was found carcinogenic in rats and mice by the CVM Cancer Assessment Committee in a July 1984 meeting In 1979 it had been regarded as a suspect carcinogen and was not approved except for emergency and Investigational use It was ordered off the market in a **letter dated Nov. 8, 1964 (Hearings,** p 424) A proposal to withdraw dibutyltin dilaurate was issued **Aug 29, 1978 but, according to an agency memo, products that contain it are still marketed under other NDAs.** Dibutyltin dilaurate is **a suspect carcinogen because it is related to dibutyltin diacetate which is carcinogenic according to NTP results. (Hearings, p 187, FDA memorandum "Re-evaluation of the Status of Certain Marketed Drugs.") The memo also mentions Ronnel which is potentially contaminated with dioxin which is carcinogenic in rats. According to the memo however, the agency did not have enough evidence to take regulatory action and recommenced requesting more data on the level of dioxin contamination in Ronnel (Hearings, pp. 188-189).**

It was also noticed **that iron dextran complex and several estrogens are regulated according to information in the *Annual Report on Carcinogens* but do not appear on the list provided by the FDA. It also appears from the hearing documents that several substances may have been regulated through informal procedures, such as Albendazole which was regulated by correspondence between the agency and** the sponsor so the **listing may not be complete.**

[b] In 1962 Congress enacted the "DES Exception to the Delaney Clause" **permitting the use of carcinogenic drugs in animals providing that they could not be detected in edible portions** of tissue or foods derived from living animals **according to methods determined by the** FDA In 1962. regulations were promulgated permitting the use of DES and establishing detection methods In the early 1970s however. the USDA found residues at levels below the sensitivity of the prescribed method

[c] The drug is regulated as a carcinogen **under the "DES** Exception, (see **footnote b), information about the identification of the drug as a carcinogen and the type** Of **evidence relied on was not** provided

[d] Gentian violet is included on the list FDA provided to OTA of compounds being considered **for regulation because of concerns about** carcinogenicity but no evidence is Cited for carcinogenic concern The FDA held that gentian **violet is not "Generally Recognized as Safe" (GRAS), however, a jury held that it is GRAS as a mold inhibitor in poultry feed up to 8 ppm *(Fed Reg.* 47 "32480) No earlier citations were** provided **According to an agency memo submitted at hearings on "The Regulation of Animal Drugs by the FDA" before a subcommittee of the Committee on Government Operations of the** House of Representatives, **July 24 and 25. 1985 (pp. 180-181) a preliminary** review **of a long-term feeding study Indicated that gentian violet is carcinogenic in mice Previously, it was only known that the main component of gentian** violet, **crystal violet, is related** to compounds that are known **animal** carcinogens and two compounds With evidence of human carcinogenicity The FDA had denied approval for its use Mar **30 1979** 4419035 and denied a hearing on the matter The decision **was** overturned on grounds that it was a disputed question as to whether gentian violet was a carcinogen *Marshall Minerals v FDA 661* **F 2d** 410 **(1** 1th Cir **3-28-80)**

[e] Ipronidazole was the subject of a causal review in 1980 **and was recommended for withdrawal** by **the Center** for Veterinary Medicine In 1983 (a causal review is an agency Procedure for reviewing safety and effectiveness data based on problems identified in reports of adverse drug reactions and serves as the basis for requesting regulatory supplemental NADAs) Concern was raised in a petition filed by the Center for Science in the Public Interest (CSPI) because instead of initiating proceedings to withdraw the drug in December 1985 it was listed among the "highest priorities for causal review A decision on the petition is pending

[f] Zeranol is a suspect Carcinogen based on a chronic bioassay of *zearalenone* ***Which*** has a Similar **structure It** is *currently* under review and chronic bioassays of *zeranol* are underway

SOURCES EPA response to OTA request and cited ***Federal Register*** notices; hearings on the 'Regulation of Animal Drugs by the FDA before the House Committee on Government Operations 99th Congress July 24 25 1985 p 66 petition to Withdraw New Animal Drug Applications submitted to the FDA by the Center for Science in the Public Interest

disease for which there is no safe therapy, it could be regarded as adequately "safe" despite major, even life-threatening, side effects, such as carcinogenicity (233). A drug manufacturer must submit an Investigative New Drug (IND) Application to conduct preliminary investigation of the safety and efficacy of the drug and a New Drug Application (NDA) for marketing approval. The NDA is to include reports of the investigation to show the drug is adequately safe and effective, a list of the drug's composition, samples of the drug, information that might be required for FDA monitoring activity, and proposed labeling.

For approved drugs, the prescription drug labeling must include a precautionary section that states the results of carcinogenicity studies. The usual type of FDA regulatory action in the drug review and approval process is to informally require the drug sponsor to modify the warning information in the physician labeling.

FDA has rarely used the more formal process of publishing a notice in the *Federal Register* to regulate drugs for carcinogenicity, as it has done for certain generic drugs or drug classes. FDA removed or the sponsor recalled from the market as active drug ingredients chloroform (1976), methapyraline (1978), and Phenacetin (1984). Precautionary labeling was instituted by this process for estrogenic drugs (1976, 1977), neuroleptic drugs except Reserpine (1978, 1980), and Reserpine (1983) (see table 3-6). FDA relied on human evidence for Phenacetin and estrogens, although positive animal evidence later became available for Phenacetin. FDA relied on animal evidence to evaluate the carcinogenicity of the other drugs.

Questions have been raised about whether FDA has always acted on positive carcinogenicity evidence in this way and whether FDA has always required sufficient information to make appropriate judgments about the safety of potentially carcinogenic drugs. For example, the House Committee on Government Operations has criticized FDA for approving Zomax as a nonsteroidal anti-inflammatory drug even though animal studies indicated a carcinogenic response, and clinical studies did not clearly show that this drug was superior to other available treatments. The committee also expressed concern that a number of other drugs of this class had been approved without adequate evidence on safety *(209).* FDA officials, on the other hand, argue that Zomax was superior to other treatments and that the animal data did not reveal a "carcinogenic" response, but rather an increase of a benign tumor type that they did not consider to be "a very alarming finding. " This increase was to be noted on the drug labeling (69).

Table 3-6.—Human Drugs Regulated as Carcinogens by FDA[a]

Substance	Type of evidence	NPRM	Final	Type of action
Chloroform	Animal	4-6-76	6-24-76	Removed from market
Methapyraline	Animal	—	6-13-78 (order)	Voluntary recall
Phenacetin	Human Animal	8-10-82 — —	10-5-83 amended 2-23-84	Removed from market
Neuroleptic drugs	Animal—rats, mice	—	5-16-78; amended 8-18-78; revised 8-8-80	Cautionary labeling; data reviewed for four drugs, but labeling required for all related drugs (except for reserpine)

[a]This table only includes drugs removed from the market or formally regulated after marketing approval. Carcinogenic drugs which require warning label are discussed in ch. 5,

SOURCE: FDA response to OTA request; cited *Federal Register* notices.

CPSC REGULATORY ACTIONS

Activated in 1973, the Consumer Product Safety Commission (CPSC) is an independent regulatory agency. Its authority to regulate carcinogens is established by both CPSA and the Federal Hazardous Substances Act (FHSA). CPSA authorizes the regulation of most consumer products that pose "unreasonable risks" of injury or illness. FHSA was initially enacted in 1960 as a labeling statute intended to fill gaps in other statutes. FHSA was later amended to permit more drastic action to control hazards and expanded "to cover hazardous substances in general use in the home, and particularly to protect children from hazardous toys and products. "

Under CPSA, when a product poses an "unreasonable risk" of injury or illness, CPSC may promulgate a consumer product safety standard, ban the product from commerce when a safety standard would not be adequate to protect the public, bring suit in Federal district court to seize an "imminently hazardous" product or seek an injunction against the distribution of the product, or require certain remedial actions. In 1981 amendments to the act, Congress required CPSC to convene a "Chronic Hazard Advisory Panel" (CHAP) prior to regulating products that present a risk of cancer, mutations, or adverse reproductive effects. Under FHSA, hazardous substances are labeled and may even be banned, but more formal rulemaking procedures are required than under CPSA.

In the 16 years since its creation, CPSC has evaluated and attempted to regulate or begun to regulate 6 individual carcinogens (vinyl chloride, 1974; tris(2,3-dibromopropyl)phosphate (tris), 1977; benzene, 1978; formaldehyde, 1981; diethyl hexyl phthalate (in process); nitrosamines, 1984) and 2 classes of carcinogens—benzidine congener dyes (begun in 1978, not pursued after 1982); and asbestos in various forms (1973, 1977) (353). (See table 3-7 for a summary.)

In 1974, CPSC banned vinyl chloride (used as a propellant in aerosols) as a hazardous substance under the FHSA. The rule was overturned on procedural grounds, but by then the manufacture of aerosols containing vinyl chloride as a propellant had ceased. For this rule, CPSC relied on the risk assessments conducted by other agencies (353). In 1977, CPSC attempted to ban the use of tris in children's sleepwear. In this case, CPSC conducted its own risk assessment. The regulatory action was overturned in court on procedural grounds, but CPSC issued a statement of policy that it was prepared to prove in court that tris products were "banned hazardous products" meriting judicial relief. CPSC brought several suits in 1977 and 1978, and its strategy was upheld (126). In 1978, CPSC proposed to ban benzene as an intentional ingredient or a contaminant in consumer products (except in gasoline and laboratory solvents), but did not finalize its proposed rule because "by 1980, in response to the Commission's action and other factors, the use of benzene in consumer products was virtually nonexistent . . . [thus] . . . The proposed ban was withdrawn in 1980" (353). In 1978, as a result of a petition, CPSC studied the carcinogenic effects of benzidine congener dyes, but concluded by 1982 that their use had virtually ceased in consumer and commercial dye markets, and thus decided no regulatory action was needed (353).

CPSC has regulated asbestos in several different products. In 1973, it banned general use garments containing asbestos (126). In 1977, it banned the use of patching compounds and emberizing materials containing asbestos (the latter was used in artificial fireplace logs), and in 1979, it negotiated voluntary agreements with hairdryer manufacturers to stop using asbestos shields in hairdryers. The agency recently issued an enforcement policy which required labeling of household products that contain intentionally added asbestos that is likely to be released in use (230).

Table 3-7.—CPSC Regulation of Carcinogens

Substance	When identified	Type of evidence	Risk assessment	Petition	NPRM	Final	Type of action	Court action
Asbestos								
—in artificial emberizing materials	—	Human, animal	yes	9-15-77 (EDF)	7-29-77	12-15-77	Banned	
—in general use garments	—	Human, animal	yes	—	—	9-27-73	Banned	
—in paper	—	Human, animal	yes	12-14-71	—		Petition granted—banned	
—in patching compounds	—	Human, animal	yes	7-15-76 (NRDC & Consumers Union)	7-29-77	12-15-77	Banned	
Benzene—in household products except motor gasoline	—	Human	yes	5-5-77 (HRG)	—	Granted	Banned	—
Benzidine—congener dyes—in household packaged dyes & dyed textiles	—	Human, animal	yes	12-18-78 (Art Hazards Project)	—	Denied	Voluntarily removed from consumer household dyes	—
Certain ingredients posing carcinogenic risk	—		—	9-8-78 (EDF)	—	Granted in part	Agreed to investigate room deodorizers and hydrocarbon aerosol propellants for toxicity and consumer exposure. test data rule	—
DEHP—as plasticizer in children's plastic articles (2-di-ethylhexylphthalate)	—	Animal, 2 species —mice, rats	yes	—	—	—	Voluntarily removed from particular children's products; agency action pending decision of adequacy of voluntary action	—
p-Dichlorobenzene	—	Animal, 1 species—mice	yes	—	—	—	Under consideration for	—
Formaldehyde —biological specimens for schools	—	—	—	—	—	—	Voluntarily reduced concentration & use	—
—in pressed wood products	—	Animal, 2 species —mice rats	yes	1-5-77 (National Land Corp.)	—	Denied	Banned	—
	—	—	—	8-11-82 (Consumer Federation of America)	—	Denied	Consensus voluntary standard activities ▫ regulate exposure levels	—
—in urea foam insulation	6-80	Animal, 2 species —mice, rats	yes	4-16-81 (Formaldehyde Institute)	6-10-80	—	Withdrawn because inadequate—would have required notice of adverse effects to potential purchasers	—
	—	—	—	10-76 (Denver D.A.'s Consumer Office)	2-5-81	4-2-82	Banned	6-14-82, stay of ban; *Gulf South Ins.* v. *CPSC*, 701 F.2d 1137 (5th Cir. 1983)—ban overturned
Methylene chloride—in aerosol paint sprays and paint strippers	—	Animal	yes	9-3-85 (Consumer Federation of America)	—		Ongoing activity ▫ determine if hazardous	—
Nitrosamines—in infants rubber pacifiers	—	Animal, several species	—	—	—	—	Less than 60 ppb (proposed voluntary standard 10 ppb per nitrosamine)	—
Perchloroethylene—in coin-operated dry-cleaning facilities	—	Animal, 2 species —mice, rats	yes	—	—	—	Under consideration for regulation	—
Tremolitic talc—in baby powder	—		—	2-9-77 (HRG)	—	Granted in part	Banned	—
Tris—flame retardant in children's sleepware	2-4-77 NCI data received	Animal, 2 species —mice, rats	yes	3-24-76 (EDF); 2-9-77 (EDF); 9-27-77 (Hilary Kam)	—	4-8-77	Labeling granted in part; ban granted in part; labeling denied; Tris treated chidren's clothing banned	*Spring Mills* v. *CPSC*, 434 F.Supp. 416 (Dist. of SC 1977)—ban overturned
Vinyl chloride—in aerosols	Noted action by other agencies	Human; animal, 3 species—rats, mice, hamsters	—	2-21-74 (HRG)	5-23-74	8-21-74; 1977	Issued order finding not safe; banned by promulgating order	*Pactra Industries Inc.* v. *CPSC*, 555 F.2d 677 (9th Cir. 1977)

SOURCES: CPSC Response to OTA request and cited *Federal Register* notices

In 1981 CPSC issued a rule banning urea-formaldehyde foam insulation (UFFI). The Court of Appeals for the Fifth Circuit struck down CPSC's ban. In particular, the court argued that because of uncertainties in the risk assessment based on an animal study, CPSC could not validly conclude that UFFI presented an unreasonable risk (see further discussion in app. A). CPSC is currently engaged in a voluntary effort with the pressed wood industry to develop national consensus standards on formaldehyde emissions from their products and has decided not to convene a CHAP at this time (286).

At present, CPSC is studying diethylhexyl phthalate (DEHP), a plasticizer in polyvinyl chloride products, and nitrosamines found in rubber pacifiers, CPSC convened a Chronic Hazard Advisory Panel in the case of DEHP; the use of DEHP in pacifiers has apparently ceased. CPSC issued a statement indicating it would bring court action under FHSA if nitrosamines in pacifiers exceed 60 ppb (353). CPSC is also working on a voluntary standard to lower the level still further (227).

Finally, CPSC is considering regulating several other carcinogens: methylene chloride, perchloroethylene, and p-dichlorobenzene. In the case of methylene chloride, CPSC is currently engaged in a proceeding to determine if it can be called a hazardous substance under FHSA. No final actions have been taken on any of these chemicals.

In attempting to regulate carcinogens, CPSC has for the most part relied on both human and animal evidence, although for tris and formaldehyde, it relied on animal evidence only (see table 3-7).

EPA REGULATORY ACTIONS UNDER THE CLEAN AIR ACT

Some of the first major environmental statutes enacted in the early 1970s were the Clean Air Act Amendments of 1970. The statute provides an elaborate Federal-State scheme for controlling conventional pollutants, such as sulfur dioxide and carbon monoxide. Because of the emphasis on controlling conventional air pollutants, toxic pollutants were almost ignored. But a provision was added authorizing EPA to set emission standards for "hazardous" air pollutants, which provide "an ample margin of safety." The general scheme is that a pollutant is first listed as hazardous based on pertinent scientific data. Then uniform national standards are to be established for each source category of such pollutants within a specified time.

However, Congress provided no explicit guidance *for* regulating carcinogens as compared with other hazardous substances under this section. This failure to address carcinogens explicitly has led to considerable controversy in interpreting the statute for application to carcinogens. For a substance with a toxic threshold, that is, a level below which there are no harmful health effects to a group of people, setting a standard would involve determining a "no effects" threshold and providing for a margin of safety. However, for carcinogens, there is no known safe threshold. Thus, providing an ample margin of safety as required by the statute might imply elimination of all exposures by setting an emissions standard of zero, or, possibly, a standard of no detectable concentrations. For these situations, where EPA determines that complete prohibition of emissions would lead to "widespread industry closure" and the costs of that closure would be "grossly disproportionate" compared to the benefits of reduced risk, EPA's strategy has been to require "emission reduction to the lowest level achievable by use of the best available control technology." Recently, however, the D.C. Circuit Court of Appeals ordered EPA to establish a safe level of emissions for vinyl chloride based on health considerations although EPA may consider cost and technological feasibility to establish the actual emission standard (28,142).

In addition, EPA has taken the position that it does not have to regulate exposures that present an "insignificant risk." This policy has been challenged in a case concerning EPA's failure to issue

benzene standards. The Natural Resources Defense Council (NRDC) argues that EPA must regulate hazardous air pollutants based exclusively on public health considerations, not technology and costs, and that EPA may not dismiss a health risk by declaring it to be "insignificant" (145).

In the nearly 16 years since enactment of CAA, EPA has listed seven carcinogens as hazardous air pollutants and issued emission standards for six carcinogens (see table 3-8): asbestos, 1973 (five source categories—amended several times); vinyl chloride, 1976 (two source categories); benzene, 1984 (for one source category, others pending); radionuclides, 1985 (four source categories); and arsenic (1986) (two source categories). Beryllium, which is classified in the *Annual Report on Carcinogens* has also been listed and regulated, although not for carcinogenic effects.[9] EPA has listed coke oven emissions (1984), and proposed emissions standards in March 1987, but has not issued them in final form.

Although CAA provides EPA 1 year in which to issue regulations on a pollutant after a substance is "listed," EPA met this deadline only in the case of vinyl chloride. From the date of listing to final action, however, EPA has taken an average of almost 4 years for the six carcinogens for which there are final rules. Four of these carcinogens were regulated or listed under legal pressure: asbestos, vinyl chloride, radionuclides, and arsenic (see table 3-8).

EPA has indicated an "intent to list" 10 substances: 1,3-butadiene, chromium, carbon tetrachloride, chloroform, ethylene oxide, ethylene dichloride, cadmium, perchloroethylene, trichloroethylene, and methylene chloride. According to EPA, an intent to list a substance as a hazardous pollutant does not legally bind the agency as does a "listing" decision (296). This position was challenged by NRDC in a pending suit (147). NRDC contends that EPA is required to list a substance immediately if it has been determined to cause serious irreversible illness and if EPA has determined that it is a hazardous air pollutant (42).

For the five substances regulated primarily for carcinogenic effects, EPA has relied on human evidence of carcinogenicity (asbestos, vinyl chloride, benzene, radionuclides, and arsenic). For 8 of the 10 substances EPA intends to regulate, it has relied on animal bioassays for evidence of carcinogenicity, and for 2 substances (chromium and cadmium), it has both animal and human evidence of carcinogenicity.

EPA's regulation of potentially hazardous air pollutants has been criticized. A report by the General Accounting Office noted that 4 of 37 hazardous substances identified for possible regulation in 1977 had been regulated by 1983 (198). The report noted both delays in issuing regulations and in obtaining Science Advisory Board approval of EPA's health assessment documents.

[9]Mercury is also regulated under the CAA, but is not classified as a carcinogen.

EPA REGULATORY ACTIONS UNDER THE CLEAN WATER ACT

First enacted in 1948, CWA has been amended numerous times, most importantly in 1972, 1977, 1981, and 1987. The 1972 act set a goal of achieving "fishable, swimmable" waters by 1983 and for prohibiting the discharge of pollutants and "toxic pollutants in toxic amounts" by 1985, although these deadlines were modified by the 1977 and 1981 amendments.

Toxic substances, including a number of carcinogens, have been regulated under CWA; but the process has taken a long time, is not yet finished, and has featured considerable litigation. The development of 65 water quality criteria documents for toxic pollutants has been an important part of EPA's risk assessment activities. While these are to be used by the States in developing State water quality standards, few such standards have actually been developed.

Under CWA, pollutors that discharge directly into receiving waters must obtain permits (Na-

Table 3-8.—Carcinogens Considered for Regulation Under the Clean Air Act

Substance	Type of evidence	Intent to list	Listed	NPRM	Final	Industrial category	Petition/court action
Acrylonitrile[d]	—	—	—	—	—	—	—
Arsenic	Human	—	6-05-80	7-20-83	*8-04-86*	High & low arsenic primary copper smelters, glass manufacturing plants–(comment period extended & reopened)	—
Asbestos	Human	—	3-31-71	12-07-71	*4-06-73*	Asbestos mills, selected manufacturing operations, spray-on asbestos materials, demolition operations, surfacing of roadways with tailings	—
Benzene	Human		6-08-77	4-18-80	—	Maleic anhydride plants	EDF petition 4-14-77
				12-18-80	—	Ethylbenzene/styrene plants	***American Petroleum Institute v EPA*** (D D C)10-4-83
				12-19-80		Storage vessels	—
				1-81	*6-06-84*	Fugitive emissions from petroleum refining & chemical manufacturing industries	3-6-84, NRDC petition denied
				3-06-84	*6-06-84*	Withdrawal of prop. stds–maleic anhydride, ethyl-benzene styrene plants & storage vessels	NRDC v *EPA* (D.D.C) 1-27-84, Court required EPA to publish final rule by 5-23-84
				6-6-84		Coke oven byproduct recovery plants	—
Beryllium[b]	Insuff. data but concerned about potential carcinogenicity	—	3-31-71	12-7-71	*4-73*	—	—
1,3-Butadiene	Animal–mice, rats	10-10-85	—		—	—	—
Cadmium	Human, animal, 1 species–rats	10-17-85	—	—	—	—	—
Carbon tetrachloride	Animal, 3 species	8-13-85	—	—		—	
Chloroform	Animal	9-27-85	—	—	—	—	—
Chromium	Human, animal	6-10-85	—	—	—	—	—
Coke oven emissions	Human, animal	4-26-82	9-18-84	4-23-87	—	Coke ovens	
Ethylene dichloride	Animal, 2 species–mice, rats	10-16-85	—	—	—	—	—
Ethylene oxide	Animal	10-2-85		—	—	—	—
Methylene chloride (dichloromethane)	Animal, 2 species–mice, rats	10-17-85	–	–	—	—	—
Perchloroethylene (tetrachloroethylene)	Animal, 2 species–mice, rats	12-26-85	–		—	—	—
Radionuclides[c]	Human	4-11-79	12-27-79	4-6-83, withdrawn 10-31-84	—	DOE facilities, NRC licensed & non-DOE Federal facilities, elemental phosphorus plants & radon-222 from underground mines	***Sierra Club v. Ruckelshaus 84-0656, 2-17-84*** (D.C.N.C.A)
				2-21-85	*4-17-85*	Radon-222 from underground mines (control technique)	*7-25-84* Court order required Agency to take final action within 90 days or find not hazardous
					2-6-85	DOE facilities, NRC licensed & non-DOE Federal facilities, elemental phosphorus plants	12-11-84 EPA held m contempt of Court, final standards required within 30 days, 120 days for radon-222 from underground mines
Trichloroethylene	Animal, 2 species–mice, rats	12-23-85	–	–	—	—	—
Vinyl chioride	Human, animal, 3 Species–rats. mice, hamsters	–	–	–	*4-26-74*	Emergency suspension of indoor aerosol pesticides	—
			12-24-75	12-24-75	*10-21-76*	ethylene dichturlae-vinyl chloride plants & polyvinyl chloride plants	—

[a] To be regulated through cooperative ventures with State and local governments (*pilot project*)
[b] Beryllium was regulated for non-carcinogenic effects, however additional evidence which indicates potential carcinogenicity is under review by EPA
[c] The proposed standards for radionuclides were withdrawn following a court order which required EPA either to promulgate the regulations within a specified period Of time or fi nd that the substances are not hazardous air pollutants EPA determined that "current practice provides an ample margin of safety to protect the public health from hazards associated with exposure to airborne radionuclides" for DOE facilities, NRC licensed & non-DOE Federal facilities & elemental phosphorus plants and issued an advanced notice of proposed rulemaking for control techniques for radon-222 emissions from underground mines. After being held in contempt, EPA issued final standards for the first three categories These standards were two and a half times higher than the originally proposed standards in order to "accommodate the current level of emissions" (quoted in the Washington Post, Jan 1, 1985, p A6)

SOURCES: EPA response to OTA request and cited *Federal Register* notices

Table 3-9.—Carcinogens Considered for Regulation Under the Clean Water Act[a]

Substance	Type of evidence	Toxic effluent standards Pro Dosed	Toxic effluent standards Issued	Number of States that issued water quality standards: Aquatic life	Number of States that issued water quality standards: Human health	Court action[b]
Acrylonitrile	Human, animal	—	—	—	—	
Aldrin/dieldrin	Animal	12-23-73 6-10-76	12-30-76	10/12	6/10	
Arsenic & compounds	Human	—	—	22	28	
Asbestos	Human	—	—	—	—	
Benzene	Human	—	—	—	—	[c]
Benzidine	Human	12-23-73 6-30-76	1-12-77	3	4	
Beryllium	Animal	—	—	7	4	
Carbon tetrachloride	Animal	—	—	—	—	[c]
Chloralkyl ethers	Animal	—	—	—	—	
Chlordane	Animal	—	—	—	—	
Chlorinated ethanes	Animal	—	—	—	—	
Chloroform	Animal	—	—	—	—	
Dichlorobenzidine	Animal	—	—	—	—	
Dichloroethylenes	Animal	—	—	—	—	[c]
Dinitrotoluene	Animal	—	—	—	—	
Diphenylhydrazine	Animal	—	—	—	—	
DDT	Animal	12-23-73[d] 6-10-76	12-30-76	—	—	
Halomethanes[e]	Animal	—	—	—	—	
Heptachior	Animal	—	—	5	3	
Hexachlorobutadiene	Animal	—	—	—	—	
Hexachlorocyclohexane	Animal	—	—	7	11	
Nitrosamines	Animal	—	—	—	—	
Polynuclear aromatic hydrocarbons	Animal	—	—	—	—	
PCBS	Animal	12-23-73 7-23-76	2-2-77	11	7	*EDF* v. *EPA, 598* F.2d 62 (D.C. Cir. 1978)
2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD)	Animal	—	—	—	—	
Tetrachloroethylene	Animal	—	—	—	—	
Toxaphene	Animal	12-23-73 6-10-76	12-30-76	—	—	*Hercules v. EPA, 598* F.2d 91 (DC Cir. 1978)
Trichloroethylene	Animal	—	—	—	—	[c]
Vinyl chloride	Human, animal	—	—	—	—	[c]

[a] Water Quality Criteria Documents were issued 11-28-80 for all substances listed except TCDD which was issued 2-15-84.
[b] All substances listed are to be regulated with technology-based standards on an industry-by-industry basis as a result of a consent decree in *NRDC* v. *Train* 8 ERC. The consent decree was incorporated into the CWA 1977 Amendments, sec. 307.
[c] *NRDC* v. *EPA* No. 85.1840 (D.C. Cir. filed 12-28-85); pertained to volatile organic chemicals.
[d] The final rule was never promulgated because EPA determined that there was insufficient evidence to promulgate responsible and defensible standards at the conclusion of a 1974 hearing.
[e] Halomethanes include chloromethane (methylchloride), bromomethane (methyl bromide), dichloromethane (methylene chloride), bromodichloromethane, tribromomethane (bromoform), dichlorodifluoromethane and trichlorofluoromethane.

SOURCES: EPA response to OTA request for information including list summarizing water quality criteria documents and *Federal Register* notices cited in above response; 40 C Sec. 129 (1984).

tional Pollution Discharge Elimination System (NPDES) permits) that delineate limitations on the amounts of conventional pollutants (e.g., biological waste material) and toxic substances allowed in discharges. NPDES permits are issued by EPA or by individual States that have an EPA-approved permit program (37 of 54 jurisdictions have been approved). NPDES permits are based on the more stringent of technology-based effluent limitations, State standards, or water quality criteria (166).

Indirect dischargers—industries that discharge into municipal sewers—are not covered under

NPDES permits, but must comply with Federal technology-based effluent limitations or local limits established under federally approved pretreatment programs. The pretreatment standards together with discharge limitations on publicly owned treatment facilities must achieve the same amount of reduction of toxic pollutants as would the use of effluent limitations on a direct discharger.

From 1972 to 1975, EPA issued, under court order, toxic effluent standards under section 307 for six pollutants: Aldrin/Dieldrin, DDT, Endrin, Toxaphene, benzidine, and PCBS. While EPA had thus begun to issue standards for toxic water pollutants on a pollutant-by-pollutant basis, several environmental groups, thinking that EPA was not regulating quickly enough, filed suit against EPA for its failure to regulate toxic pollutants. At the same time industry groups were concerned that a pollutant-by-pollutant approach would require different standards for different pollutants without regard for the availability or compatibility of various strategies of control (79).

Under pressure from both groups, EPA developed a technology-based strategy for regulating pollutants on an industry-by-industry basis. The suits were settled in a consent decree (the "Flannery decree") with EPA agreeing to place specific "numerical limits on the quantities of *65* toxic pollutants in 21 industrial categories" (62,79). The consent decree permitted EPA to regulate toxic substances by means of those sections of CWA designed to control ordinary nontoxic pollutants, and to regulate pollutants on an industry-by-industry basis using effluent limitations (79).

Provisions of this consent decree were incorporated into CWA by Congress in the 1977 amendments, thereby giving congressional sanction to the development of technology-based regulations on toxic pollutants. One result is that under CWA, similar-sounding terms have different meanings. An effluent standard is a control re*quirement* based on the relationship between the discharge of a pollutant and the resulting water quality in a receiving body of water. An effluent limitation, on the other hand, is a technology-based approach. For example, use of BPT, BAT, or "best conventional technology, " might be required for direct dischargers.

Effluent limitations are what are used today. EPA has been in the process of issuing technology-based effluent limitations for 65 categories of toxic substances.

The 65 classes of pollutants were chosen in the negotiations leading to the consent decree. For choosing these classes of pollutants, EPA assembled a working group of staff scientists from EPA and other agencies (78). This group conducted a literature search for toxic pollutants using several criteria: 1) evidence that a substance posed potential carcinogenic, mutagenic, teratogenic effects, or adverse effects on any organ system; and 2) evidence of persistence, ability to bioaccumulate in organisms, and synergistic propensities. These general criteria yielded 337 organic compounds, which the committee narrowed to 232. Using the criteria of presence in water effluents and evidence of carcinogenic, mutagenic, or teratogenic effects in animal tests or human epidemiology, or evidence of high toxicity to aquatic organisms or systems, the list was further narrowed to 76. From this list of 76, EPA provided more specific lists of 29, 18, and 18 classes of substances. [10]

List I of 29 classes of substances satisfied three criteria:

1. they were known to occur in point source effluents, in aquatic environments, in fish, or in drinking water;
2. there was substantial evidence of carcinogenicity, mutagenicity, and/or teratogenicity in human or animal studies; and
3. it was likely that point source effluents contributed substantially to human exposure, at least locally.

List II of 18 compounds of second highest priority satisfied the first criterion, but toxicity evidence was based primarily on structural similarity to compounds on list I, mutagenicit, tests, or test results that appeared to be incomplete or equivo-

[10] EPA originally developed a fourth list of 12 substances. Although they are present in water effluents, they were judged to present a less substantial direct hazard than the chemicals on lists 1-111 and were not included in the final list of substances to be regulated.

cal. The 18 compounds on list III all satisfied the first criterion, but there was no substantial evidence that these compounds have "primary carcinogenic, mutagenic, or teratogenic effects" (78). (See table 3-10 for these lists.)

These 65 classes of pollutants, also known as priority pollutants, initially contained more than 129 individual substances, but EPA developed a list of 129 specific substances (177). Three of these were removed from the list, leaving a total of 126 individual substances in 28 industrial classes for which it had to set regulations.[11]

As of today, EPA has issued regulations for 26 of the 28 industry groups. Regulations for the pesticides industry had been issued, but that regulation was challenged in court, and EPA has remanded the regulation and initiated work to develop new regulations for the pesticide industry. The organic chemicals, plastics, and synthetic fibers industry has yet to be regulated, even though it contributes the largest quantity of organic pollutants of any industry *(224).*

Moreover, the 28 industry groups do not cover all industries that discharge pollutants. Important industries, such as car washes and other commercial laundries, and paint and ink formulators are excluded completely from effluent guidelines and pretreatment standards. Certain subcategories of other industries, such as adhesives and sealants, are also exempted. Pretreatment standards (for indirect dischargers) were proposed for some in-

[11]The exact number of "industries" has varied because definitions were changed.

Table 3-10.-Classes of Substances Regulated Under the CWA Consent Decree

List I	List II	List III
1. Acenaphthene	1. Chlorinated benzenes (other than dichlorobenzenes)	1. Acrolein
2. Aldrin/dieldrin	2. Chlorinated ethanes	2. Acryionitrile
3. Arsenic compounds	3, 2-chlorophenol	3. Antimony compounds
4. Asbestos	4. Dichloroethylenes	4. Chlorinated naphthalene
5. Benzene	5. 2,4-Dichlorophenol	5. Chlorophenols (those not on list 11)
6. Benzidine	6. 2,4-Dimethylphenol	6. Copper compounds
7. Beryllium compounds	7. Dichloropropane and dichloropropene	7. Cyanides
8 Cadmium compounds	8. Endosulfan and metabolizes	8. Dinitrotoluene
9 Carbon tetrachloride	9. Endrin and metabolizes	9. Ethylbenzene
10. Chlordane (technical mixture and metabolizes)	10. Fluoranthene	10. Hexachlorocyclo-pentadiene
11. Chloroalkyl ethers	11. Haloethers (not on list 1)	11. Isophorene
12. Chloroform	12. Halomethanes (not on list 1)	12. Nitrobenzene
13. Chromium compounds	13. Hexachlorobutadiene	13. Nitrophenols
14, DDT and metabolizes	14. Naphthalene	14. Phenol
15. Dichlorobenzenes (1,2-,1,3-, and 4-dichlorobenzenes)	15. Pentachlorophenol	15. Selenium compounds
16. Dichlorobenzidine	16. Phthalate esters	16. Silver compounds
17. Diphenylhydrazine	17. Tetrachloroethy lene	17. Toluene
18. Heptachlor and metabolizes	18. Toxaphene	18. Zinc compounds
19. Hexachlorocyclohexane		
20. Lead compounds		
21. Mercury compounds		
22. Nickel compounds		
23. Nitrosamines		
24. Polychlorinated biphenyls (PCBS)		
25. Polynuclear aromatic hydrocarbons		
26. 2,3,7,8-Tetrach lorodibe nzo-p-d ioxi n (TCDD)		
27. Thallium compounds		
28. Trichloroethylene		
29. Vinyl chloride		

SOURCE: Office of Technology Assessment.

dustries, such as textile mills, and plastics molding and forming, but were never issued (224).

The standards that have been issued cover the list of 126 chemicals, although not all 126 chemicals are regulated in each of the 28 industry groups. For each industry, EPA has issued regulations for the pollutants that it judged appropriate to regulate. In a given industry, a particular chemical may not be present, may have no available treatment technique, may be too costly to control, or maybe "incidentally" covered by regulations for other pollutants.

While the list of 126 chemicals has been the focal point of the regulation under CWA, many of the chemicals found in industrial effluents are not included in this list. In a nationwide study of wastewater from a wide variety of industries and publicly owned treatment works (POTWs), 4,000 wastewater samples were examined for organic pollutants using gas chromatograph-mass spectrometry. The result is an overall picture of the chemicals discharged by these industries and POTWs. After ranking the top s0 most frequently occurring compounds, the researchers discovered that 16 of them were priority organic pollutants. Thus, 34 of the s0 most frequently occurring compounds are not included in the EPA list of priority pollutants. For the industries studied, the distribution of pollutants differed by industry (i.e., what is important for one industry may not be important in another industry). In general, the priority pollutants make up approximately 25 percent of the most frequently occurring compounds (185).

In addition to setting the technology-based effluent limitations, EPA is also authorized to issue nonbinding water quality criteria documents (under section 304) for substances that might pose hazards to human health or the environment. These are used to guide States in setting water quality standards in their water courses (under section 303) and as guidance for writing NPDES permits. As of 1986, EPA had issued water quality criteria for 65 classes of priority toxic pollutants, including 29 determined to be carcinogenic. These are listed in table *3-10*,[12]

[12]*The list* of substances in the table was derived from a list EpA provided that summarizes the water quality criteria documents. OTA included in the table only those substances that were indicated to be carcinogens. Some substances that appear in the ***Annual Report on Carcinogens*** have been regulated under CWA, but do not appear on this table because the water quality criteria were not based on carcinogenic effects.

The water quality criteria documents present information on protecting human health and aquatic organisms (fish, shellfish, plants, etc.). For human health, the criteria are developed to protect against noncarcinogenic risks as well as carcinogenic risks and are based on two potential exposure pathways—through consumption of drinking water and aquatic organisms. Because safe thresholds for exposure to carcinogens have not been established, the recommended criteria for the maximum protection of human health are water concentrations of zero. But EPA also prepared quantitative risk estimates for carcinogens. The published criteria include the concentrations of the chemical in water that corresponded to calculated lifetime cancer risks of 10^{-5}, 10^{-6}, and 10^{-7}.

States have the option of adopting these numerical **criteria,** but not all of them have actually done so. Water quality criteria have been prepared for the 65 classes of toxic pollutants covering 126 chemicals—the priority pollutants. For 37 of the 85 organic chemicals from this list, no States have developed standards; for another 32, one State has developed standards. Less than half of the States have developed a water quality standard for any single priority pollutant except arsenic for which standards were established in 28 states (345). Fourteen States have no water quality standards at all for any of the priority pollutants (224). As table 3-10 shows, seven of the water quality criteria that identify chemicals as carcinogenic have been adopted by at least one State.

Although the environmental groups who brought the original suit that resulted in the Flannery decree believed that regulating toxic pollutants by means of technology-based effluent limitations would speed the elimination of these from the Nation's waterways, the regulation has taken *con*siderable time. EPA has missed deadlines and has requested eight separate deadline extensions from the court. EPA's most recent goal of regulating all pollutants for all industries by January 1987 **was not** achieved. EPA now hopes to complete

the effluent limitations specified in the original 1976 consent decree by September 1987 (166).

In addition, the compliance dates for the industries are usually 3 years after EPA publishes its final rule on the BAT regulations. Thus, even though the consent decree was issued in 1976, not all industries will be in compliance with the regulations until the late 1980s or 1990.

Under the 1987 Amendments to CWA, each State is required to submit to EPA a list of "toxic hot spot waters." These are areas where water quality standards cannot be achieved or maintained because of toxic discharges after the currently required pollution controls have been implemented. The States must also submit a plan to bring these areas into compliance with those standards. The State water quality standards must be based on EPA water quality criteria for toxic pollutants.

EPA REGULATORY ACTIONS UNDER THE SAFE DRINKING WATER ACT

The Safe Drinking Water Act of 1974 regulates the safety of water from public water systems, and it contains several provisions that may be used to regulate hazardous substances, including carcinogens in drinking water. SDWA authorized EPA to regulate contaminants "which . . . may have an adverse effect on the health of persons, " and prescribed several steps for EPA to follow.

First, EPA was required to publish national interim primary drinking water standards in 1975. Second, Congress required that EPA commission the National Academy of Sciences (NAS) to "conduct a study to determine . . . the maximum contaminant levels which should be recommended" as national standards. NAS was also required to update this information every 2 years. The NAS study had to consider the impact of contaminants on groups or individuals in the population who are more susceptible to adverse effects than are normal health individuals, exposure to contaminants in other media, synergistic effects of contaminants, and body burdens of contaminants in exposed persons. In its 1977 report, *Drinking Water and Health,* (134) NAS provided its first list of contaminants (chosen on the basis of its own criteria) that might have an adverse effect on health and the levels at which those effects are expected based on the best available scientific knowledge. The NAS report, however, did not provide recommended contaminant levels.

Third, within 90 days of the publication of the NAS study, EPA was required to establish "recommended maximum contaminant levels (RMCLs) for each contaminant which . . . may have any adverse effect on the health of persons. " Each such RMCL was to be "set at a level at which . . . no known or anticipated adverse effects on the health of persons occur and which allows an adequate margin of safety. " RMCLs were nonenforceable health goals which were then used as guidelines for establishing enforceable drinking water standards.

Once EPA established RMCLs for each contaminant, it was required to publish revised national primary drinking water regulations. These regulations were enforceable health standards. The required regulations were to specify a maximum contaminant level (MCL) or require the "use of treatment techniques" for each contaminant for which an RMCL is established. The established MCLs were to be as close to the RMCLs as is "feasible. " In determining feasibility, the Administrator could consider "the use of the best technology, treatment techniques and other means . . . [that] are generally available [taking cost into consideration] ."

Drinking Water Standards

Under its authority to set drinking water standards, in 1975 EPA promulgated interim drinking water standards for 10 inorganic and 6 organic chemicals and for microbial contaminants (40 CFR 141.11-141.14). The interim drinking water standards issued in 1975 were based on the 1962 recommendations of the U.S. Public Health Service (214).

Among the inorganic, arsenic was specifically cited as being of concern because of carcinogenicity, although EPA decided that the evidence for its carcinogenicity in drinking water was inconclusive. (See table 3-11 for a summary of these data.) Among the organic compounds, endrin, lindane, and toxaphene were regulated based on the effects of acute and chronic exposure, but the substances were later identified as carcinogens by the NAS Drinking Water Committee and by EPA in subsequent proposed drinking water standards. In addition, EPA issued regulations for two groups of carcinogens: radionuclides in 1976 (40 CFR 141.15) and for total trihalomethanes (four chemicals) in 1979 (40 CFR 141.31).

Thus, the initial approach under SDWA was to issue standards contaminant by contaminant, specifying that every public water system monitor for each contaminant to ensure compliance with the standard. However, it would be both costly and technologically difficult to monitor for relatively small amounts of many synthetic organic compounds and other potentially toxic con-

Table 3.11 .—Carcinogens Regulated and Proposed for Regulation Under the Safe Drinking Water Act (SDWA), Actions Before 1980

Substance	Type of evidence[a]	ANPR	NPRM	Final
Inorganics:[b]				
Arsenic	Human, inconclusive	—	3-14-75	12-24-75
Cadmium	—	—	3-14-75	12-24-75
Chromium	—	—	3-14-75	12-24-75
Lead	—	—	3-14-75	12-24-75
Nitrate/nitrite	—	—	3-14-75	12-24-75
Selenium	—	—	3-14-75	12-24-75
Organics:[c]				
Chlorinated hydrocarbons:				
Aldrin/dieldrin	—	—	[d]	Not issued
Chlordane	—	—	3-14-75	Not issued[e]
DDT	—	—		Not issued
Endrin	—	—	3-14-75	12-24-75
Heptachlor	—	—	3-14-75	Not issued
Heptachlor epoxide	—	—	3-14-75	Not issued
Lindane	—	—	3-14-75	12-24-75
Toxaphene	—	—	3-14-75	12-24-75
Total trihalomethanes[f]				
Bromodichloromethane	Inadequate/ suspected	7-14-76	2-9-78	11-19-79
Dibromochloromethane	Inadequate/ suspected	7-14-76	2-9-78	11-19-79
Tribromomethane (bromoform)	Inadequate/ suspected	7-14-76	2-9-78	11-19-79
Trichloromethane (chloroform)	Animal, 2 species (rats, mice)	7-14-76	2-9-78	11-19-79
Radionuclides:				
Radium 226 & 228	Human, animal	—	8-14-75	7-9-76
Gross alpha particle activation	Human, animal	—	8-14-75	7-9-76
Beta particle & photon radioactivity	Human, animal	—	8-14-75	7-9-76
Treatment standard for all synthetic organic chemicals:[g,h]		*7-14-76*	*2-9-78*	Withdrawn

[a]Type of evidence was derived from the Federal *Register* notices that presented EPA's rationale for regulatory action.
[b]According to the NPRM, the MCLs for inorganic were based on the "possible effects Of lifetime exposure." Specific carcinogenic concerns were cited only in response to the comments on arsenic.
Carcinogenic evidence was not cited. The MCLs were based on the "effects of acute and chronic exposure."
[d]Carcinogenic concerns were mentioned but action was delayed pending the results of a nationwide survey to determine the extent of drinking water contamination by these substances
[e]Carcinogenic concerns were mentioned but final action was delayed pending outcome of FIFRA Suspension/Cancellation proceedings.
[f]Formed as the result of chlorination Of drinking water.
[g]Treatment techniques were proposed for all synthetic organic chemicals (SOCs) as a class rather than individual MCLS because it was not considered feasible to identify and monitor individual substances. Carcinogenic concerns were based on an NAS report, "Drinking Water and Health" which identified 22 SOCS (listed below) as known or suspected carcinogens.
[h]Court challenge: *EDF* v, Costle, 11 ERC 1209, No. 752224, 2-10-78.

SOURCE: EPA response to OTA request and cited *Federal Register* notices.

taminants that might occur in drinking water coming from surface water sources. So in 1978 EPA proposed treatment regulations for drinking water systems that used surface waters. The focus was on generic treatment techniques for all synthetic organics without requiring monitoring of numerous individual contaminants.

The proposal for a treatment standard was withdrawn, however, because EPA could not find a clear basis for selecting communities with a synthetic organic chemical contamination problem that would be required to use the treatment techniques. There was also concern about cost and feasibility. Moreover, by 1980 emphasis shifted from surface to ground water contamination. Because of this, EPA began again to focus on setting health standards using a contaminant-by-contaminant approach, rather than pursuing the goal of setting treatment standards for surface water (36).

The contaminants were grouped for the purpose of regulation into volatile synthetic organic chemicals (VOCs), synthetic organic chemicals (SOCs), inorganic chemicals, microbiological contaminants, radionuclides, and disinfectants. This change in approach, from a contaminant-by-contaminant approach to surface water treatment standards and back to the contaminant-by-contaminant approach, delayed the issuance of revised national primary drinking water standards.

In March 1982 EPA issued an Advance Notice of Proposed Rulemaking (ANPRM) for nine VOCs (303). It then held workshops around the country and in June of 1983 issued proposed RMCLs for VOCs (300). It issued final RMCLs for VOCs and proposed MCLs for VOCs in November 1985 (301). Eight final MCLs for VOCs were issued in June 1987 (322).

For 31 SOCs, 16 inorganic compounds (IOCs), radionuclides, and microorganisms, EPA first issued an ANPRM in October 1983 (304), followed by proposed RMCLa in November 1985 (302). Except for fluoride (which is not a carcinogen), EPA has yet to issue final RMCLs, proposed MCLs and final MCLs on these chemicals. In addition, EPA must address a number of the 83 substances for regulation under the requirements of the 1986 amendments.

To determine the RMCLs for carcinogens, EPA classified substances into three categories based on the evidence for carcinogenicity —strong evidence (Category I), equivocal evidence (Category II), and inadequate evidence or lacking evidence (Category III). Classification into these categories for the drinking water standards is based largely on the the classification of the substance in the EPA weight-of-evidence classification (see ch. 2).

Category I chemicals have strong evidence for carcinogenicity from either human or animal studies, i.e., weight-of-evidence group A (sufficient evidence for human carcinogenicity) or group B (probable human carcinogen, based either on limited human evidence or sufficient animal evidence). Category I substances have RMCLs of zero. EPA chose this level for RMCLs based on the legislative history of SDWA (301). MCLs for Category I substances must be set as close to zero as is feasible, taking costs into consideration.

Category II chemicals, with equivocal evidence for carcinogenicity for purposes of drinking water standards, are chemicals including weight-of-evidence group C (possible human carcinogens based on limited evidence in animals). Category III chemicals, those with inadequate evidence or lacking evidence for carcinogenicity, are from weight-of-evidence group D (not classified or inadequate animal evidence) or group E (no evidence for carcinogenicity).

Category II substances have RMCLs set in one of two ways. The first, and preferred approach is to set the RMCLs based on noncarcinogenic chronic toxicity data. Under this approach, EPA calculates an Adjusted Acceptable Daily Intake (AADI). The second method, used when adequate chronic toxicity data are lacking, is to base the RMCLs on the results of quantitative risk assessment using the limited animal carcinogenicity data with the risk level set in the range 10^{-5} to 10^{-6}.

Category 111 substances have RMCLs based on noncarcinogenic chronic toxicity data. Again EPA calculates an AADI.

For either Category 11 or Category III chemicals, EPA determines, on the basis of chronic toxicity data, a highest “no observed adverse effect level” (NOAEL) (expressed in mg/kg body weight/day),

divides that figure by an appropriate "uncertainty" or "safety" factor (explained below), then multiplies this figure by the assumed weight of an adult (70 kg) and divides by the assumed amount of water consumed by an adult (2 liters/day). The result is an AADI:

AADI = (NOAEL/uncertainty factor) (70kg/2Liters/day)

A safety or uncertainty factor of 10 is "used with valid experimental results on appropriate durations of exposure in humans." A safety factor of 100 is "used when human data are not available and extrapolating from valid results of long-term studies in animals" is involved. A safety factor of 1,000 is "used when human data are not available and extrapolating from studies in animals of less than chronic exposure." Finally, an additional uncertainty factor between 1 and 10 is used when EPA has to use a "lowest observed adverse effect level" (LOAEL) rather than a NOAEL (151,299).

Since Category 11 substances have some limited if insufficient evidence of carcinogenicity from animal studies, EPA introduces additional safety or uncertainty factors to account for the equivocal evidence of carcinogenicity. Normally, a safety factor of 10 is used, but if data indicate the need for a greater or lesser safety margin, other uncertainty factors can be used (301). In general EPA is more cautious in setting RMCLs and MCLs for Category II substances than for Category III substances.

In its regulatory proceedings so far, five of the nine VOCs were identified as probable carcinogens (Category I). EPA's decision to consider one of them, 1,1-dichloroethylene, as belonging to category 11 was legally challenged by NRDC and a decision is pending (158). Of 32 SOCs, 10 are probable carcinogens. Of the inorganic substances, two (arsenic and asbestos) were placed in Category II. These substances are carcinogenic when inhaled. EPA has concluded, however, that *there is* little evidence indicating that asbestos is carcinogenic in drinking water. There is evidence that drinking water exposures to arsenic are associated with skin cancer, although it appears that this is true only for the generally nonfatal forms of skin cancer (36). For the 15 Category I chemicals, 2 were based on human data, and the balance on animal evidence. In addition, all the radionuclide standards were based on human data (see table 3-12).

Health Advisories

In addition to legally binding regulations, EPA has also provided nonbinding health advisories for contaminants in water. In 1980 the National Academy of Sciences began providing EPA with "suggested no adverse response levels" (SNARLS) for contaminants. These contained acute (24-hour exposure) and short-term (7-day exposure) toxicity information as well as chronic toxicity information. The Office of Drinking Water developed its own SNARLS and issued drafts of them beginning in 1981. Subsequently the term SNARLS was changed to "health advisories" (HAs).

HAs are approximately 10-page dossiers on chemicals that give some indication of their occurrence, their use, short-term toxicity information, chronic toxicity information (including contaminant levels calculated to be associated with different levels of risk, e.g., 1 case per 10,000 people exposed, 1 case per 100,000 people, 1 case per 1 million people), analytical methods of detecting them, and treatment methods that operators of municipal water systems can use. Health advisory concentration numbers are "developed from data based on non-carcinogenic endpoints of toxicity." For suspected carcinogens "non-zero l-day, 10-day and longer-term health advisories may be derived . . . [but] lifetime exposures may not be recommended." In addition, "projected excess lifetime cancer risks are provided to give an estimate of the concentrations of the contaminant which may pose a carcinogenic risk to humans." These estimates are presented as "upper 95 percent confidence limits derived from the linearized multistage model which is considered to be unlikely to underestimate the probable true risk" (325).

EPA issued its first HAs in 1979, reevaluated them in 1985, and rereleased some *52* for public comment and for evaluation by the EPA Science Advisory Board *(36).* Health advisories are not legally binding, but are intended to advise public water systems about the health effects of chemicals and their treatment. Health advisories have been widely used in the water industry to determine responses to contamination incidents (36).

Table 3-12.—National Primary Drinking Water Regulations (NPDWR) for Carcinogens, Actions After 1980

Substance	EPA classification & type of evidence	Recommended maximum contaminant level (RMCL)			Maximum contaminant level (MCL)	
		ANPR	NPRM	Final	NPRM	Final
Inorganics (not regulated as carcinogens):						
Arsenic [a]	II	10-5-83	11-13-85	—	—	—
Asbestos	II	10-5-83	11-13-85	—	—	—
Cadmium	III	10-5-83	11-13-85	—	—	—
Chromium	III	10-5-83	11-13-85	—	—	—
Lead	III	10-5-83	11-13-85	—	—	—
Nitrate/nitrite	III	10-5-83	11-13-85	—	—	—
Selenium	III	10-5-83	11.13-85	—	—	—
Synthetic organics:						
Acrylamide	I, animal	10-5-83	11-13-85	—	—	—
Alachlor	I, animal	10-5-83	11-13-85	—	—	—
Chlordane	I, animal	10-5-83	11-13-85	—	—	—
Dibromochloropropane (DBCP)	I, animal	10-5-83	11-13-85	—	—	—
1,2-Dichloropropane	III animal	—	11-13-85	—	—	—
Epichlorohydrin	I, animal	—	11-13-85	—	—	—
Ethylenedibrornide	I, animal	—	11-13-85	—	—	—
Heptachlor	I, animal	—	11-13-85	—	—	—
Heptachlor epoxide	I, animal		11-13-85	—	—	—
Lindane	II, animal	10-5-83	11-13-85	—	—	—
Monochlorobenzene	III	—	11-13-85	—	—	—
Polychlorinated biphenyls (PCBs)	I, animal	—	11-13-85	—	—	—
Styrene	II[b]	—	11-13-85		—	—
Toxaphene	I, animal	10-5-83	11-13-85	—	—	—
Volatile organic compounds:						
Benzene	I, human		6-12-84	*11-13-85*	11-13-85	—
Carbon tetrachloride	I, animal	3-4-82	6-12-84	11-13-85	11-13-85	—
p-dichlorobenzene	III, animal	—	6-12-84	11-13-85	11-13-85	—
1,2-Dichloroethane	I, animal	3-4-82	6-12-84	11-13-85	11-13-85	—
1,1-Dichloroethylene	II, animal	—	6-12-84	11-13-85	11-13-85	—
Tetrachloroethylene	II, animal	3-4-82	6-12-84	[c]	—	—
1,1,1 -Trichloroethane	III, animal	3-4-82	6-12-84	11-13-85	11-13-85	—
Trichloroethylene	I, animal	3-4-82	6-12-84	11-13-85	11-13-85	—
Vinyl chloride	I, human, animal	3-4-82	6-12-84	11-13-85	11-13-85	—
Radionuclides:						
Radium 226 & 228	Human	10-5-83	—	—	—	—
Gross alpha particle activation	Human	10-5-83	—	—	—	—
Beta particle & photon radioactivity	Human	10-5-83	—	—	—	
Uranium	Human	10-5-83	—	—	—	—
Radon	Human	10-5-83	—	—	—	—

[a] The proposed regulation was not based on carcinogenic effects because it was considered also to have potential nutrient value.
[b] Proposed regulation not based on carcinogenic effects.
[c] Comment period reopened to consider new data, 11-13-85

SOURCES: EPA response to OTA request and cited *Federal Register* notices.

Regulation of carcinogens in drinking water has been slow. The SDWA was passed in 1974. As indicated above, in 1975 interim standards based on Public Health Service recommendations of 1962 were issued, and later radionuclides (1976) and trihalomethanes (1979) were regulated. These standards are still in effect today.

As of June 1987, EPA has issued eight final MCLS that constitute national revised primary drinking water standards. Revised HAs designed to provide operators of public water systems with guidance concerning health risks from potential toxic substances are not yet final, although they are under development.

The 99th Congress, concerned that drinking water standards were not being set quickly enough, set regulatory deadlines in the 1986 re-authorization of SDWA.

The 1986 SDWA amendments (Public Law 99-339) required EPA to regulate 83 chemicals in drinking water that the agency had identified as candidates for regulation in 2 ANPRMs in 1982 and 1983 (303,304). The list of 83 are to be regulated in 3 stages by 1989 and include 51 in the process of regulation. EPA must also add 25 chemicals to the list every 3 years after 1989. According to EPA staff, this list of 83 included numerous substances that EPA had not otherwise intended to regulate because of low toxicity or low occurrence in drinking water (36).

The 1986 amendments gave RMCLs a new name: Maximum Contaminant Level Goals (MCLGs). The criteria for these remain the same as for the RMCLs. In addition, MCLs must now be proposed at the same time as the MCLGs rather than in two stages as they were previously. The MCL must be as close to the MCLG as is feasible using the BAT, taking costs into consideration. It must be at least as low, however, as would be achieved using granulated activated carbon (an especially good technique for removing organic contaminants). When an MCL is exceeded, the public must now be notified within 14 days of the detection of the violation.

In addition, the amendments required EPA to develop a list of unregulated contaminants which water utilities must monitor at least once every 5 years. A list of 50 unregulated chemicals for which monitoring will be required is scheduled for publication in June 1987 (36). Congress also authorized stricter enforcement of SDWA and increased fines for violations.

EPA REGULATORY ACTIONS UNDER FIFRA

The Federal Insecticide, Fungicide, and Rodenticide Act was substantially amended in 1972. Under this act, EPA is to screen pesticides through the registration process before they enter commerce and reregister pesticides that were on the market before 1972 to prevent unreasonable adverse health and environmental effects. In both cases, EPA may require manufacturers to submit testing results for product and residue chemistry, environmental fate, and tests in fish, wildlife, and mammals, including long-term bioassays for carcinogenicity.

An applicant for registration of a pesticide must file with EPA certain required information, including a statement of all claims made for the pesticide, directions for its use, a description of tests made upon it, the test results used to support claims made for the substance, and appropriate toxicity data for each pesticide. Specific testing requirements depend on the expected use pattern. EPA now requires carcinogenicity testing in two species for all food use pesticides (40 CFR 158).

In general, EPA must register a pesticide if "it will perform its intended function without unreasonable adverse effects on the environment"-which are defined as "any unreasonable risk to man or the environment, taking into account the economic, social and environmental costs and benefits of the use of any pesticide. " The burden of proof to establish the safety of a product lies on the person who wishes to register and market the product.

If EPA finds that a registered pesticide meets or exceeds certain criteria for risk, a special review may be initiated. (Prior to 1983, this was called a "Rebuttable Presumption Against Registration" (RPAR).) This in-depth review of the risks and benefits of the pesticide use determines what regulatory action, if any, is appropriate. The 1975 amendments to FIFRA require that if involuntary regulatory measures are proposed, the EPA recommendations must be submitted to the Department of Agriculture for comment and to the FIFRA Scientific Advisory Panel for review. There is also an opportunity for public comment throughout this process. The outcome of a special review can range from no action, to an immediate emergency suspension, to cancellation of the pesticide. Actions may also consist of modifying the use pattern of the pesticide.

Unless the data on which the special review or RPAR is based are shown to be unreliable or invalid, or the estimated benefits of continued uses

outweigh the estimated risks, FIFRA provides for cancellation or suspension of their registration.

In 1972, there were about 50,000 pesticide products and 600 active ingredients already on the market that required reregistration under the new law. Many of the problems of regulating pesticides have arisen with these pesticides. The aim of reregistration was to identify missing information about pesticides, to require registrants to supply it, and to reevaluate the safety of the chemicals in light of the new information. Reregistration involves a number of steps:

1. EPA requests certain pivotal studies on the chemical from the registrant ("data call-in") if studies have not yet been submitted. Data requirements are based on EPA regulations (40 CFR 158). Since 1980, EPA has required carcinogenicity data for reregistration where required (40 CFR 158).
2. EPA reviews all available data on the chemical, including that requested in the data call-in.
3. EPA issues a "regulatory position document" ("registration standard") which summarizes the science position, changes in use necessary to reduce risk, and additional data gaps.
4. Registrant either agrees to fill data gaps or action may be initiated to withdraw the chemical from the market.
5. If "significant risk triggers" are identified in steps-2 through 4, a special review is initiated (21).

The reregistration of active ingredients has taken much longer than originally anticipated. The process was initially to be completed by 1976, but in 1975 Congress extended that deadline to 1977, and in 1978 dropped the deadline completely because of the large number of substance reviews outstanding (203).

The EPA data files for most of the pesticides needing reregistration are still incomplete, although information is currently under development. EPA conducted a data call-in for approximately 600 active ingredients subject to reregistration. As a result of data call-ins, by March 31, 1986, 61 active ingredients had been canceled voluntarily, withdrawn, or suspended, and 124 interim registration standards developed. Of these 124 active ingredients with registration standards, 6 were voluntarily withdrawn, while 12 were beginning special reviews, and 17 were ready for final regulatory review, while 89 registrants' responses were in progress. One active ingredient is undergoing final standard processing, which would result in final reregistration (203).

Thus, for 72 percent of the chemicals reviewed sufficiently to develop registration standards (89 of 124), EPA is currently waiting to obtain necessary data. Beyond this, over two-thirds of all active ingredients (415 of 600) have not yet been reviewed sufficiently for the agency to issue even registration standards.

Of the 600 active ingredients, about 390 are used on foods. EPA has completed its data call-in for all 390 substances and has issued interim registration standards on 92, with approximately 300 yet to be evaluated. EPA lacked sufficient information to judge the carcinogenic effects of 57 of these 92 ingredients (203).

Actions on Pesticides Already Identified as Carcinogenic

For some 80 active ingredients that have been voluntarily removed from the market or subject to some regulatory activity, carcinogenicity has been an important element. In all, 65 of these 80 substances (81 percent) have had carcinogenic effects.[13]

OTA requested information from EPA on the pesticides it has identified as carcinogenic. As of March 31, 1986, it had identified at least 81 carcinogens. (See tables 3-13 to 3-16 for a summary of these data.)14 These carcinogens were identified through testing results obtained from a variety of sources, including manufacturers and NTP, and reported in the open literature.

- Of the 81, 18 have been canceled or restricted for some or all uses as a consequence of EPA action (table 3-13).

[13] The percentages are based on the information in "Report on the Status of Chemicals in the Special Review Program, Registration Standards Program, and Data Call-in Program" (331).

[14] ThiS count of chemicals is slightly different from that in other sources of information, including EPA status reports, GAO reports, and correspondence between EPA and Congressman Waxman.

- For one, Daminozide (Alar), EPA published a notice of intent to cancel, but the chemical is still undergoing review (table 3-13).
- Fifteen pesticides have been voluntarily canceled by the registrant (table 3-14).
- At present, 18 of these substances are in special review (SR) (table 3-15). For 10 carcinogens, the SRs have been completed but the chemicals have not been suspended or canceled because EPA decided to allow their continued use based on the balance of risks and benefits (104). For the remaining eight substances, SRs have yet to be completed.
- EPA has identified 29 carcinogens for which it has not started an SR or cancellation proceeding (table 3-16). Of these, 24 are food use pesticides.

Tables 3-15 and 3-16 together indicate that EPA has identified 47 carcinogenic pesticides that have not been canceled. Of these, 18 were made the subjects of SRs (10 completed, 8 still in progress); for others, EPA has decided not to conduct an SR. For example, for 13 of the 47, EPA has determined that either low exposure or risk or the weight of the evidence for carcinogenicity suggest no action need be taken. The remaining identified carcinogenic pesticides are still in use, although EPA suggested to OTA that for many of these regulatory action has been taken to reduce exposure (21). These actions may consist of requiring lowered application rates, enclosed application systems, extension of reentry intervals, a ban on aerial application, and protective equipment and clothing (104).

Moreover, "cancellation" of the 18 chemicals on table 3-13 does not mean that the chemical is no longer in use. Often, a cancellation is for particular uses, while other uses continue. For example, chlordane was canceled in 1978 for food use (table 3-14), but continues in use for termite control. EPA is currently considering whether to cancel that use as well.

For the 18 substances that have been canceled or restricted by EPA (table 3-13), the average time carcinogens were in SR was 44 months, with the shortest time being 13 months and the longest 88 months. Substances in SR earlier took the shortest time with more recent cancellations taking longer. For 10 carcinogens in SR, but not suspended or canceled, the average length of the SR was 63 months, with the shortest SR 36 months and the longest 106 months.

Where EPA has acted on carcinogenic pesticides, the evidence for carcinogenicity has generally been based on positive results from at least two animal species (tables 3-13 to 3-16).

According to figures in a recent NAS report (136), of 289 food use pesticides, 53 or approximately 18 percent have been determined by EPA to beat least potentially carcinogenic. However, for many of these the data are still incomplete or have not been evaluated. Food use pesticides raise special issues with regard to coverage under FDCA.

For raw agricultural commodities, a tolerance for pesticide residues is based on the consideration of risks and benefits (under sec. *408* of FDCA). If processing the food leads to an increase in the concentration of the pesticide residue to a level above that found in the parent raw commodity, then the Delaney clause applies (sec. 409 of FDCA). In this case, the residue is deemed to be a food additive and may not be added to food if it is determined to be carcinogenic. Congress specifically exempted processed food from the Delaney clause if the residue level is no higher than is found in the raw commodity. For commodities that are processed, if no section 409 tolerance may be granted, EPA will not grant a 408 tolerance for the raw commodity either.

While the Delaney clause has been consistently used to deny new tolerances for active ingredients, it has never been used to revoke an existing tolerance. Prior to 1978, section 408 tolerances were generally established without any oncogenicity or residue data. Few of the pesticides approved before 1978 have tolerances for residues in processed foods. Where no tolerance exists for a processed food, EPA simply assumes that residue levels are the same as the level permitted in raw commodities. In the report, the NAS committee concluded that there is no scientific justification for the regulatory distinction between raw and processed foods. The committee also found no scientific justification for the inconsistency between the safety standards applied to old and new pesticides (136).

Table 3-13.—FIFRA[a]
I. Canceled and Restricted Carcinogenic Pesticides

Substance	Registration standard	Type of evidence	Special review initiated	Proposed determination	Notice of intent to cancel/suspend	Voluntary cancellation/ some or all uses	Comments/other regulatory action	Court action or administrative hearing
Aldrin/	—	Animal, 2 species — mice, rats	—	—	3-18-71; 6-28-72, susp.; 10-18-74, canc.(most uses)	—	—	Shell Chem. Co. et al., FIFRA Doc. #145; EDF petition filed 12-3-70; *EDF* v. *EPA*,465 F2d 528 (DC Cir. 1972) re: suspension pending outcome of hearing
Amitraz (Baam)[b]	9-85	Animal, 2 species	4-6-77	0-7-79			Conditional registration, for use on pears, not apples	—
Arsenicals (inorganic)[b]	—	Animal, human	10-18-78 wood & non-wood uses	7-13-84 wood use	7- 3-84 wood use	—	Labeling requirements	In re: Chapman Co., et al. FIFRA Doc. #529, 7-15-84
copper acetoarsenite					—	4-7-77	—	—
copper arsenate	—	—	—	—	—	4-7-77	—	—
arsenic trioxide	—	—	—	—	—	6-19-78	—	—
sodium arsenite	—	—	—	—	—	10-18-7[illegible]		—
Chlordane, heptachlor	—	Animal, 2 rats	—	—	7-29-75 susp.; 3-24-78 canc. food uses	8-87 non-food uses	Agreement to discontinue sales unless studies conducted show no residue from outside use	Velsicol Chem. Co. et al., FIFRA Doc. #384, 336; *EDF* v. *EPA*, 548 F 2d 998 (D.C. Cir. 1976) (EDF petition 10-74); *NCAMP et al.* v. *EPA*, CIV 87-2089 LFO (D.C. Cir. filed 8-24-87)
Chlordecone	—	Animal, 2 species	3- 9-76	4-11-77	4-[illegible]1-77 all uses	7-27-77	—	Lethelin Products Co., et al., FIFRA Doc. #392, re: cancellation 4-11-77
Chlorobenzilate[b]	12-83	Animal, 2 species	5-26-76	7-11-78	12- 3-79	—	Canceled all uses except citrus	—
Coal tar and creosote								
Daminozide (Alar) [b c]	6-1-84	Animal, 2 species	8-18-84	9-12-85	2-1 -86	—	Labeling requirement	
DBCP	—	Animal, 2 species— rats, mice	9-22-77	1-9-85	1-8-77 susp. some uses; 7-18-79 susp. all uses; 11-9-79 susp. all uses— withdrawn 3-31-81; 1-12-84 canc. all uses	3-31-81 voluntary canc. all uses except pineapple	Partial susp. 11-3-77; all uses except pineapple susp. 10-29-79; all uses canc. 1-9-85	Shell Oil Co. et al., FIFRA Doc. #401 & 485
DDT/DDD	—	Animal, 1 species— mice	1969, (USDA review)	—	1969, some uses; 7-7-72, all uses	—	—	Stevens Industries et al., FIFRA Doc. # 63; *EDF* v. *EPA*, 439 [illegible].2d 584 (DC Cir. 1971)
Dinitramine	—	Animal	—	—	9-28-82	—	—	—
EDB	—	Animal, 2 species	2-14-77	9-28-83	9-28-83 pending hearing; 2-3-84 susp. grain use	—	Revoked exemption from tolerance; 2-22-84 proposed tolerance grain, citrus papaya, 3-6-84	Vulcan Chem. Co. et al., FIFRA Doc. # 503, re: cancellation; *NCAMP et al* v. *EPA*, No. 86-1114 (DC Cir. filed 2-14-86), re: tolerance

continued on next

Table 3-13.—FIFRA[a]
1. Canceled and Restricted Carcinogenic Pesticides—Continued

Substance	Registration standard	Type of evidence	Special review initiated	Proposed determination	Notice of Intent to cancel/suspend	Voluntary cancellation/ some or all uses	Comments/other regulatory action	Court action or administrative hearing
Endrin	—	Animal, 2 species	7-27-76	11-2-78	7-25-79 most uses	10-24-84 Other uses	–	—
Goal [e] (product of oxyfluorfen, contaminated with PCE)	–	Animal, 2 species	1-80	6-23-82	6-23-82	—	Limited concentration of PCE	—
Mirex	—	Animal, 2 species	—	—	3-18-71, 9-23-76 cane all uses	—	5-3-72 labeling restrlctions, 6-30-72 reinstated registrations under certain conditions, 4-4-73 modified ban on aquatic application	Allied Chemical Co., FIFRA Doc #293, 10-20-76, re: cancellation— 2-12-76 registrant submitted phase-out plan to settle hearing, *McGill v EPA,* 593 F.2d 631 (5th Cm. 1979)
Pentachlorophenol[e] (contaminated with Dioxin)	—	Animal	10-18-78	7-13-84 wood use, 12-12-84 non wood uses	7-13-84 wood uses	—	Labeling & restricted use requirements	In re. Chapman Co et al , FIFRA Doc #529, 7-15-84, re Cancellation
Pronamide (Kerb)	4-86	Animal 1 species—mice	5-20-77	1-15-79	10-26-79	—	Restricted use & labeling required	—
Toxaphene[b c]	—	Animal, 5 species–rats, mice, dogs, monkeys, hamsters	5-25-77	11-29-82	11-29-82		Canceled for most uses	—
2,4,5 -T/Silvex	—	Animal, 2 species	4-21-78	12-13-79	3-15-79 susp. some uses, 1-2-85 susp. all uses	—	—	In re: Dow Chemical Co , et al , FIFRA Dec. #409/410, re: emergency suspension, FIFRA Doc #415, re cancellation, 3-1-79; Doc *Chemical Co v Blum*, 469 F, Supp. 892 (E D Mich. 1979)

[a] These tables contain only active pesticide ingredients In addition to the listed substances, EPA has identified 28 inert Ingredients Of concern for potential carcinogenicity among 55 inerts Of concern for Inherent toxicity (as Of 6- 19-85) The agency is evaluating these inerts to determine the extent of use and exposure whether they are essential whether safer alternatives are available, and what regulatory actions would be appropriate The 28 inert Ingredients of carcinogenic concern are– aniline diethylhexylphthalate (DEHP) *asbestos benzene, betabutyrolactone cadmium* compounds carbon tetrachloride chlorobenzene chloroform 12-dichloropropane dimethyl 11hydrazine 12 dioxane epichlorohydrin ethylene dichloride ethylene thiourea formaldehyde hexachlorophene hydrazine isophorone methylene chloride 2-nitro-propane perchloroethylene phenylphenol propylene oxide rhodamine thiourea 1 1 1 -tri-chloroethane (methyl chloroform) trichloroethylene

[b] Regulated under Sec 408 FDCA Registered for food uses–tolerances established for pesticide uses on raw agricultural commodities

[c] Regulated under Delaney Clause of FDCA Sec **409(c)(3)(A)** A food additive tolerance is required when [he pesticide residue level in processed food IS greater than the tolerance level for the raw agricultural commodity but may not be established for carcinogenic pesticides

[d] According t. EPA these compounds d. not have oncogenic effects but they have a metabolite that has shown oncogenic effects In animals

[e] According t. EPA thes, compounds do not have oncogenic effects but they contain a contaminant that has shown oncogenic effects in animals

SOURCE EPA response to OTA request and cited *Federal Register* notices

Table 3-14.—FIFRA[a]
II. Voluntary Cancellations of Carcinogenic Pesticides

Substance	Registration standard	Type of evidence	Special review initiated	Proposed determination	Notice of intent to cancel/suspend	Voluntary cancellation/ some or all uses	Comments/other regulatory action	Court action or administrative hearing
Acrylonitrile	—	Animal	–	—	—	9-1-76	3 products	—
Benzene	—	Human	–	—	—	7-31-85	All products	
BHC	—	Animal, 2 species	10-19-76	10-19-76	—	10-19-76, manufacturing only, began to import	7-21-78 amended registration to replace non-gamma Isomer content with Lindane	—
Carbon tetrachloride	–	Animal, 2 species	10-15-80	–	—	9-5-83	—	—
Chloranil	—	Animal	–	—	—	1-19-77	—	—
Erbon	—	Animal	–	—	—	10-4-80	—	—
Maleic hydrazide[b,c]	–	Animal, 1 species–mice	10-28-77	6-28-82 terminated	—	11-81 some uses	Returned to registration process	—
Monuron	6-83	Animal	–	—	—	8-16-77	Tolerance revoked m 1973	—
Nitrofen (TOK)	—	Animal	–	—	—	9-15-83	—	—
OMPA	—	Animal	–	—	—	5-28-76	.	.
Perthane	—	Animal	–	—	—	6-20-80	—	—
Safrole	—	Animal	–	—	—	2-25-77	—	—
Strobane	—	Animal, 1 species	–	—	—	6-28-76	All products	—
2 , 4 , 5 -Trichlorophenol	–	Animal	9-15-78	12-31-85	—	All uses, no date	—	—
Trysben	—	Animal	–	—	—	2-9-78	—	—

[a]These tables contain only active pesticide Ingredients in addition to the listed substances, EPA has identified 28 inert ingredients of concern for potential carcinogenicity among 55 inerts Ot concern for inherent toxicity (as of 6-19-85) The agency is evaluating these inerts to determme the extent of use and exposure, whether they are essential whether safer alternates are available, and what regulatory actions would be appropriate The 28 inert Ingredients of carcinogenic concern are—aniline diethylhexylphthalate (DEHP); asbestos, benzene, betabutyrolactone; cadmium compounds, carbon tetrachloride; chlorobenzene; chloroform, t ,2-dichloropropane; dimethyl 1,1 hydrazine 1,2 dioxane epichlorohydrin; ethylene dichloride; ethylene thiourea formaldehyde, hexachlorophene hydrazine isophorone; methylene chloride 2-nitro-propane; perchloroethylene; phenylphenol; propylene oxide rhodamine thiourea 1 1 1-tri-chloroethane (methyl chloroform) trichloroethylene

[b]Regulated under Sec 408 FDCA Registered for food uses–tolerances established for pesticide uses on raw agricultural commodities

[c]Regulated under Delaney Clause of FDCA Sec 409(c)(3)(A) A food additive tolerance is required when the pesticide residue level m processed food is greater than the tolerance level fOr the raw agricultural commodity but may not be established for carcinogenic pesticides

SOURCE EPA response to OTA Request and cited *Federal Register* notices

Table 3-15.—FIFRA[a]
II. Carcinogenic Pesticides in Special Review
(A. Presently under review)

Substance	Registration standard	Type of evidence	Special review initiated	Proposed determination	Notice of intent to cancel/suspend	Voluntary cancellation/ some or all uses	Comments/other regulatory action	Court action or administrative hearing
Alachlor[b]	11-21-84	Animal, 2 species	1-9-85	—	—		Labeling requirement, restricted use	—
Amitrole	3-30-84	Animal	6-15-84	—	—	—	Labeling requirement, restricted use	—
Cadmium	—	Animal, human	10-26-77	—	—	—	—	—
Captafol[b]	10-84	Animal, 2 species	12-9-84			—	Labeling requirement; restricted use	—
Captan[b c]	3-86	Animal, 2 species	8-18-80	6-21-85 proposed determination	—	—	—	—
Ethylene oxide[b]	–	Animal–insufficient but positive short-term test (in 1978)	1-27-78	—	—		—	—
Kelthane (Dicofol)[b] (contains DDT)	12-83	Animal, 1 species–mice (see DDT)	3-21-84	10-10-84, proposed cane.	—	—	—	—
Linuron[b]	*7-84*	Animal, 2 species	9-26-84	—	—		Labeling requirement	

[a] These tables Contain only active pesticide ingredients In addition to the listed substances, EPA has identified 28 inert ingredients of concern for potential carcinogenicity among 55 inerts Of concern for Inherent toxicity (as Of 6-19-85) The agency is evaluating these inerts to determine the extent of use and exposure, whether they are essential, whether safer alternates are available, and what regulatory actions would be appropriate The 28 inert ingredients of carcinogenic concern are—aniline diethylhexylphthalate (C) EHP); asbestos, benzene, betabutyrolactone; cadmium compounds; carbon tetrachloride; chlorobenzene; chloroform, 1,2-dichloropropane; dimethyl 1,1 hydrazine 1,2, dioxane; epichlorohydrin; ethylene dichloride; ethylene thiourea formaldehyde, hexachlorophene hydrazine; isophorone; methylene chloride, 2-nitro-propane; perchloroethylene; phenylphenol; propylene oxide, rhodamine; thiourea; 1,1,1 -tri-chloroethane (methyl chloroform), trichloroethylene

[b] Regulated under Sec 408 FOCA Registered for food uses–tolerances established for pesticide uses on raw agricultural commodities

[c] Regulated under Delaney Clause of FDCA Sec 409(c)(3)(A) A food additive tolerance is required when the pesticide residue level in processed food IS greater than the tolerance level for the raw agricultural commodity but may not be established for carcinogenic pesticides

SOURCE EPA response to OTA request and cited *Federal Register* notices

Table 3-15.—FIFRAa
III. Carcinogenic Pesticides in Special Review
(B. Special review complete but substance not suspended or canceled)

Substance	Registration standard	Type of evidence	Special review initiated	Proposed determination	Notice of intent to cancel/suspend	Voluntary cancellation/ some or all uses	Comments/other regulatory action	Court action or administrative hearing
Benomyl[b c]	4-86	Animal, 1 species—mice	12-6-77	10-20-82	—	—	Labeling requirements; restrictions on conditions of application	—
Chloroform (trichloromethane)	12-82	Animal	4-6-76	12-82 terminated SR			More data required, exposures reduced with label changes	—
Diallate[b]	3-83	Animal, 2 species	5-31-77	6-23-82	—	—	Labeling requirements, training & protective clothing	—
Dimethoate	3-31-83	Animal, 2 species	9-22-77	1-19-81		—	—	—
EBDCs[b c]	—	Animal, 2 species	8-10-77	10-27-82	—	—	More data required, labeling requirement	—
Ethalfluralin[b]	—	Animal, 1 species	1-4-84	1-4-84	—	—	Tolerances issued, protective clothing requried	
Lindane[b]	9-85	Animal, 1 species	2-18-77	9-30-83	—	—	More data required, restricted use	In re: Happy Jack Inc. & Continental Chemist Corp. FIFRA Doc. #524 & 526, 10-19-83, re: cancellation
PCNB[b]	—	Animal, insuff	10-13-77	*4-28-82* terminated SR	—	—	4-19-82, negotiated agreement to reduce exposures	—
Thiophonate methyl[b d]	5-86	Animal, 1 species—mice	12-7-77	10-20-86		—	Label precautions	—
Trlfluralin[b c] (contaminated with n-nitrosamine)	—	Animal	8-30-79	8-4-82	—	—	Limit set for amount of n-nitrosamine	—

[a] These tables contain only active pesticide ingredients in addition to the listed substances EPA has identified 28 inert Ingredients of concern for potential carcinogenicity among 55 inerts Of concern for inherent toxicity (as of 6- I 9-85) The agency is evaluating these inerts to determine the extent of use and exposure, whether thev are essential, whether safer alternatives are available and what regulatory actions would be appropriate The 28 inert ingredients of carcinogenic concern are —aniline diethylhexylphthalate (DEHP); asbestos benzene, betabutyrolactone cadmium compounds carbon tetrachloride chlorobenzene chloroform 1 2-dichloropropane dimethyl 1 1 hydrazine 1 2 dioxane epichlorohydrin ethylene dichloride ethylene thiourea formaldehyde hexachlorophene hydrazine isophorone, methylene chloride 2-nitro-propane, perchloroethylene phenylphenol propylene oxide rhodamine thiourea 1 1 1-tri-chloroethane (methyl chloroform) trichloroethylene

[b] Regulated under Sec 408 FDCA Registered for food uses–tolerances estabhshed fOr pesticide uses on raw agricultural commodities

[c] Regulated under Delaney Clause of FDCA Sec 4139(C)(3)(A) A food additive tolerance is required when the pesticide residue level in processed food is greater than the tolerance level for the raw agricultural commodity but may nOt be established for carcinogenic pesticides

[d] According to EPA, these compounds do not have oncogenic effects but they have a metabolite that has shown oncogenic effects in animals

SOURCE EPA response to OTA request and cited *Federal Register* notices

Table 3-16.—FIFRA[a]
IV. Pesticides Identified as Carcinogenic But Not Reviewed or Canceled

Substance	Registration standard	Type of evidence	Comments/other regulatory action
Acephate [bc]	I-86 (pub. draft)	Animal	
Acetochlor	—	—	Under review for oncogenic potential
Acifluorfen [b]	—	—	No action taken because EPA determined that exposure/risk from use patterns is below level for concern
Amdro [b]	—	—	No action taken because EPA determined that exposure/risk from use patterns is below level for concern
Asulam [b]	Under development	(Potential carcinogen)	—
Azinphos methyl (Guthion) [b]	Under development	(Potential carcinogen)	—
Chlordimeform [bc]	I-86 (pub. draft)	Animal	
Chlorothalonil [b]	10-84	Animal	More data required; labeling requirement
Cypermethrin [b]	—	—	EPA determined that weight of evidence for carcinogenicity does not support regulatory action
Cyromazine (Larvadex) [bc]	—	—	No action taken because EPA determined that exposure/risk from use patterns is below level for concern and that weight of evidence for carcinogenicity does not support regulatory action
Diclofop-methyl (Hoelon) [b]	—	—	No action taken because EPA determined that exposure/risk from use patterns is below level for concern
Dimethipine (Harvade) [b]	—	—	No action taken because EPA determined that exposure/risk from use patterns is below level for concern and that weight of evidence for carcinogenicity does not support regulatory action
Fenarimol	—	—	Under review for oncogenic potential
Folpet [b]	Under development	(Potential carcinogen)	
Fosetyl al (Aliette)b	6-30-83	Animal	—
Glyphosate [b]	6-86	Animal	—
Methanearsonic acid [bc]	—	invalid study	EPA determined that weight of evidence for carcinogenicity does not support regulatory action
Methomyl	9-81	Animal	Manufacturing process restrictions; labeling requirement; restricted use
Metolachlor [b]	9-80	Animal	—
Oryzalin [bc]	Pub. draft	Animal	
Oxadiazon [b]	—	—	No action taken because EPA determined that exposure/risk from use patterns is below level for concern
Paraquat [bc]	4-86	Animal	Pre-SR completed 6-29-82, returned to registration process
Parathion [bc]	Under development	(Potential carcinogen)	—
Permethrin [b]	—	—	EPA determined that weight of evidence for carcinogenicity does not support regulatory action
Terbutryn [b]	Under development	(Potential carcinogen)	Pre-SR agreement 5.12-82; label changes to reduce applicator exposure
Thiodicarb (Larvin) [bc]	—	—	EPA determined that weight of evidence for carcinogenicity does not support regulatory action

[a] These tables contain only active pesticide ingredients. In addition to the listed substances, EPA has identified 28 inert ingredients of concern for potential carcinogenicity among 55 inerts of concern for inherent toxicity (as of 6-19-85). The agency is evaluating these inerts to determine the extent of use and exposure, whether they are essential, whether safer alternatives are available, and what regulatory actions would be appropriate. The 28 inert ingredients of carcinogenic concern are—aniline, diethylhexylphthalate (DEHP); asbestos; benzene; betabutyrolactone; cadmium compounds; carbon tetrachloride; chlorobenzene; chloroform; 1,2-dichloropropane; dimethyl 1,1 hydrazine 1,2; dioxane; epichlorohydrin; ethylene dichloride; ethylene thiourea; formaldehyde; hexachlorophene; hydrazine; isophorone; methylene chloride, 2-nitropropane; perchloroethylene; phenylphenol; propylene oxide; rhodamine; thiourea; 1,1,1-tri-chloroethane (methyl chloroform); trichloroethylene

[b] Regulated under Sec. 408 FDCA. Registered for food uses—tolerances established for pesticide uaes on raw agricultural commodities.

[c] *Regulated* under Delaney Clause of FDCA Sec. 409(c)(3)(A). A food additive tolerance is required when the pesticide residue level in processed food is greater than the tolerance level for the raw agricultural commodity but may not be established for carcinogenic pesticides.

[d] According t. EPA, these compounds do not have oncogenic effects, but they have a metabolize that has shown oncogenic effects in animals.

[e] According t. EPA, these compounds do not have oncogenic effects, but they contain a contaminant that has shown oncogenic effects in animals

SOURCES: EPA response to OTA request for information, EPA correspondence with Representative Henry Waxman (10-2-85); EPA Office of Pesticide Programs, March 1988, "Report on the Status of Chemicals in the Special Review Program, Registration Standards Program, and Data Call-in Program;" GAO, April 1986, "Pesticides-EPA's Formidable Task to Assess to Regulate their Risks" GAO/RCED-86-1 25; EPA, "Suspended, Cancelled & Restricted Pesticides" Third Revision, January 1985; *Federal Register* notices for each action provided information on the type of evidence used

Other Pending Issues

In addition to its focus on active ingredients, EPA regards about 55 inert ingredients as "high concern," with 28 of these showing carcinogenic effects. Another 51 substances have "suspected toxicity" while between 800 and 900 other inert ingredients have insufficient health and safety data (130,203). In April 1987, EPA issued a policy statement announcing the intent to encourage the use of the least toxic inert ingredient available, require data necessary to determine the conditions under which it may safely be used, and hold hearings to determine whether the use of certain inert ingredients should continue to be permitted. EPA also intends to reclassify some of them as active ingredients (294).

EPA has inadequate information on a number of nonagricultural pesticides to determine health risks, and these pesticides have not been reassessed by the current standards (202). After reviewing the status of EPA's chronic toxicity data for 50 chemicals, selected because they are used in large quantities, the General Accounting Office found that "EPA had done preliminary assessments for 18 of the 50 nonagricultural chemicals [pesticides not used on crops] and found that it did not have enough chronic toxicity data on 17 of the 18 chemicals to complete the assessments." A tiered approach (explained below in the section on TSCA) in obtaining chronic test data on nonagricultural pesticides is currently taking place through the data call-in (21).

Finally, EPA has invalid or fraudulent health data on 36 pesticides, including 35 food use pesticides. Some or all of these products may have been tested by Industrial Biotest Laboratories, which submitted invalid, and in some cases fraudulent, test data in the mid-1970s (203,206). These data are being replaced through the data call-in and reregistration process.

EPA REGULATORY ACTIONS UNDER TSCA

The Toxic Substances Control Act was enacted in 1976. With TSCA Congress established the policy that chemical manufacturers are responsible for developing data about the health and environmental effects of their chemicals, that the government regulates chemical substances that pose unreasonable risks of injury to health or the environment, and that regulatory efforts should not unduly impede industrial innovation. Singled out for special concern were substances that present or will present significant risks of cancer, gene mutations, or birth defects.

EPA actions under TSCA cover both new and existing chemicals. For new chemicals, the principal focus is a premanufacturing review. After review of available information, EPA can request or require additional toxicity testing, can require certain workplace practices and controls, and can require that the manufacturer notify EPA before putting the chemical to a "significant new use." For existing chemicals, EPA can require testing for toxicity and environmental effects, designate the chemical for priority review, require that "significant new uses" be reported, require manufacturers, importers, and processors to report production and use information, or require that they submit copies and lists of unpublished health and safety studies to EPA. EPA can also issue regulations restricting or banning the production of a chemical or limiting its uses.

New Chemicals

Under section 5 of TSCA, chemical manufacturers must submit a premanufacturing notice (PMN) for any "new chemical." "New chemicals" are those not found in the TSCA inventory of chemicals in commerce. At the end of EPA's review, any one of four actions are possible:

1. The substance described in the PMN can be manufactured without restriction.
2. The substance can be manufactured for the uses described in the PMN, but the Agency can require that it be notified if manufacture for a significant new use is considered. If EPA decides that a potential new use of the substance might be associated with an unreasonable health or environmental risk, it

can by a separate rulemaking procedure issue a Significant New Use Rule (SNUR) to restrict the manufacture or distribution of the substance (section 5(a)(2)).

3. The manufacture, processing, distribution, use or disposal of the new substance can be regulated pending the development of additional information about the substance (section 5(e)).
4. The manufacture, processing, distribution, use, or disposal of the new substance can be regulated because it presents or will present an unreasonable risk (section 5(f)) (222).

From July 1979, when the program started, until September 1986, EPA received 7,356 valid PMNs (see table 3-17). EPA decided that no further action was necessary for 5,761 of these, or about 80 percent. Of the remaining chemicals that raised EPA concerns, 523 were subject to some kind of action. EPA concerns led to the manufacturers' agreeing to voluntary testing in 64 cases, voluntary control actions such as the use of personal protective equipment in 33 cases, and the complete withdrawal of the PMN in 139 cases. Thus, in 236 cases or about 45 percent, the threat of EPA action lead to informal, "voluntary" responses by the manufacturers. The other half of the time the actions were more formal: 271 chemicals subject to consent orders under which the manufacturers agree to controls for worker exposure, or restrictions on production use or disposal until testing is done (section 5(e)); 12 unilateral orders under which EPA imposes restrictions or bans pending until testing is completed (section 5(e)); and 4 chemicals subject to immediately effective proposed rules setting permanent requirements for the production of these chemicals (sections 5(f) and 6(a)). EPA has received notices of commencement of manufacture for 3,678 of the 7,356 chemicals.

In 1983, OTA prepared a background paper, *The Information Content of Premanufacture Notices,* describing the nature and extent of information reported on PMNs submitted during a 2-year period from 1979 to 1981, and on PMNs submitted for June of 1982. That study found that about half the submitted PMNs reported no toxicity information and "only 17 percent of PMNs have any test information about the likelihood of the substance's causing cancer, birth defects or mutations—three biological effects that *were* singled out for special concern in TSCA" (222). Because long-term experiments in whole animals are expensive, the tests conducted for all these PMNs were short-term mutagenicity tests.

Table 3-17. -TSCA: New Chemicals, Section 5 PMN Reviews

	Total (1979-86)
Valid PMNs received	7,356
PMNs requiring no further action	5,761
Some action	523
Voluntary testing	64
Voluntary control actions	33
PMNs voluntarily withdrawn	139
Section 5(e) consent orders	271
Unilateral 5(e) orders	12
Section 5(f) rules	4
New chemicals subject to SNUR:	
Proposed	55
Final	15

SOURCE: EPA response to OTA request for information

The submitters of nine of the PMNs examined by OTA did not begin manufacture because of EPA actions. Six of the substances were phthalates, of special concern because of a recent National Cancer Institute study showing some phthalates to be carcinogenic (222). Two of the remaining three were benzidine dyes, which have long been associated with human carcinogenicity. The submission of these PMNs shows that substances of demonstrated toxicity, even substances closely related to known carcinogens, are still considered for possible manufacture and use.

Because most PMNs do not contain any toxicity test information, EPA is forced to rely on structure-activity relationships in attempting to predict, from the chemical structure of the substance, the hazards it poses. In this case, EPA uses computerized databases on chemical structures to identify related chemicals or analogs. EPA then searches toxicity databases for information on the analogs. EPA staff admit that the identification of analogs is a "rather subjective process, " and that the final assessments concerning a new chemical rely on the "knowledge and professional judgments" of the staff performing the evaluation (11).

Existing Chemicals—Obtaining Additional Data

Section 4(e) of TSCA created an Interagency Testing Committee (ITC) to review existing chemicals and make recommendations to EPA about testing chemicals for health and environmental effects. EPA is to review these recommendations and then decide whether testing should or should not be required. TSCA provides that ITC shall give "priority attention" to chemicals that cause or are suspected of causing cancer, mutations, or birth defects. ITC can simply commend a substance or mixture to EPA's attention, or ITC can "designate" it, in which case EPA has 12 months to initiate a proceeding to require testing or publish reasons for deciding that testing is unnecessary.

The recommendations are in the form of a list of chemical substances and mixtures. This "Priority List" of "designated" chemicals awaiting EPA action at any one time cannot exceed so.

By statute, ITC consists of representatives from EPA, OSHA, NIOSH, the National Institute of Environmental Health Sciences, the National Cancer Institute, the National Science Foundation, the Council on Environmental Quality, and the Department of Commerce. In addition, seven other agencies belong to ITC as "liaison members": CPSC, FDA, NTP, the U.S. Department of Agriculture, the U.S. Department of Defense, the U.S. Department of the Interior, and the National Library of Medicine. They participate in the reviews of chemicals and the meetings of ITC, although they do not vote to select the chair of ITC or on the contents of the final reports.

TSCA specifies a number of factors for ITC to consider in designating substances and mixtures:

- the quantity that is or will be manufactured,
- the quantity that enters or will enter the environment,
- the extent of occupational exposures (both numbers of workers and durations of exposure),
- the number of people exposed (presumably including people exposed outside the workplace),
- the similarity to other substances known to present unreasonable risks to health or the environment,
- the existence of data on health and environmental effects,
- the extent to which testing may result in data useful for predicting effects on health or the environment, and
- the availability of testing facilities and personnel (sec. *4 (e)).*

Using a periodic process called a "scoring exercise, " ITC narrows down the universe of chemicals in commerce (over 50,000) in several steps to select a manageable number (40-so) for detailed review by ITC members. The most recent scoring exercise—the sixth, completed in January 1987—began with a list of approximately 20,000 organic chemicals. The first step was to remove chemicals previously reviewed by ITC, as well as common metabolizes, chemicals "generally recognized as safe (GRAS), " food additives, drugs, pesticides, certain regulated chemicals, and widely occurring natural products. The remaining chemicals on the master list were then arrayed in different lists based on potential health effects, potential ecological effects, presence in the environment, potential high workplace exposures, and potential high consumer exposure. Each chemical then received a "score" based on the frequency of occurrence on these lists. Chemicals not produced or imported in significant quantities were removed, and the remaining substances were scored for exposure potential, health effects, and ecological effects. From these scores, chemicals were selected for more detailed review by ITC. More detailed information was prepared for these chemicals, and then ITC made its recommendations to EPA (335). A major problem in this process is the difficulty of obtaining current data on the volumes of domestic production and imports (16).

ITC transmits an updated list of recommended substances to EPA at least every 6 months. These reports are published in the *Federal Register* for public comment. The first ITC report was published in October 1977; report number 19 came out in November 1986.

EPA's responses to the ITC lists have generated concern, both for the length of time they have taken to develop responses and for the procedures

chosen for obtaining the necessary test data. During the first years of the program, from the first ITC report in 1977 until the sixth in November 1980, EPA never responded within the statutory deadline of 12 months. Because of this failure to act, NRDC sued EPA. In a decision in early 1980, a New York District Court ruled that EPA had failed to fulfill its responsibilities to act on ITC-designated chemicals. As a result, for reports 7 through 16, EPA has responded within the deadline for all designated chemicals (195).

At the time of the initial lawsuit, EPA also developed a new procedure to negotiate agreements with chemical manufacturers concerning the conduct of toxicity tests. These negotiated testing agreements were designed to avoid what EPA viewed as the difficulties of the rulemaking procedures mandated by TSCA. Six hundred studies were produced under 22 of these agreements (341).

In 1983, EPA was sued a second time by NRDC, on the grounds that TSCA did not provide for these voluntary negotiated testing agreements and that such agreements did not trigger certain other provisions of the law. The court agreed and ordered EPA to reconsider its decisions on several chemicals. In 1985, NRDC and the Chemical Manufacturers Association (CMA) approached EPA concerning these issues. The result was a new set of EPA procedures under which EPA attempts to negotiate a consensus among all interested parties on testing needs. If negotiation fails, EPA will develop a test rule. In either case, EPA appears committed to the prompt resolution of these issues, i.e. meeting the statutory deadline (338).

In 1985, ITC created a "recommended with intent-to-designate" category for chemicals it intends to designate in the future. This new category enables EPA to begin gathering production and use data, and information on unpublished health and safety studies (see discussion below), before the statutory l-year clock starts ticking. EPA regards this category as essential for using the negotiated consent agreement process since negotiations require an additional 10 weeks (341). Any information obtained in this way can also be reviewed by ITC before making the final decision to "designate" the chemical.

Counting the total number of chemicals recommended by ITC and considered by EPA is difficult, because a single recommendation may cover a single chemical or a group of chemicals. In the 19 reports published through September 1986, ITC has recommended testing for 101 chemicals or groups of chemicals. Of these, 94 were "designated. "[15] Counting all of the discrete chemicals in the various groups of chemicals under consideration yields a total of 389 chemicals (17,18).

In all, EPA has issued 20 final rules on testing for various health and environmental effects (not necessarily carcinogenicity). Another 24 proposals for test rules are pending, and 5 chemicals or chemical groups have been the subjects of ANPRMs. Finally, for 51 chemicals or chemical groups, EPA has decided that testing is not needed ("decisions not to test"), and for 1 category, EPA returned the category to ITC (195).

Table 3-18 presents the 17 chemicals from the ITC reports for which EPA has required, proposed, or negotiated carcinogenicity testing. These include 11 chemicals to be tested in carcinogenicity bioassays and 6 tested in "tiered testing, " which involves conducting a battery of short-term tests and then evaluating the results before deciding whether to require a long-term bioassay.

EPA can require testing under section 4 for chemicals in addition to the ones recommended by ITC, but this has been less frequent than consideration of ITC-recommended chemicals. Recent proposals concerning 1,1-dichloroethylene, diethylene glycolbutyl ether, 2-ethylhexanol, and a group of 73 substances found at hazardous waste sites are the exceptions. The latter two were nominated by other program offices at EPA, the Air Office and the Office of Solid Waste and Emergency Response, respectively. This may mark the beginning of a new trend, but thus far the testing agenda under TSCA has been set by ITC and its recommendations. According to EPA this is because, under section 4(e), ITC designations have top priority, and, also because of resource limitations (341).

[15] In the 19th report, two additional chemicals were recommended with "intent-to-designate. " The 94 "designated" chemicals include three that had been similarly recommended with "intent-to-designate" in reports 17 and 18.

Table 3-18.—TSCA: Existing Chemicals; Testing Required To Determine Carcinogenicity

Name	ITC nomination date of Federal publication	Negotiated testing agreement	NPR	Final	Type'
Alkyl phthalates	10-12-77	1-5-82	[a]	—	c
Benzyl butyl phthalate	11-25-80	1-5-82	*9-6-85*	Pending[b]	c
Antimony trioxide	6-1-79	9-2-83	[c]	—	c
Aryl phosphates	4-19-78	—	12-19-83 (ANPR)		T
2-(Butoxyethyl) ethyl acetate	12-14-83	—	8-4-86	Pending	c
Chlorinated benzene	10-12-77		1-13-84	7-8-86	c
4-Chlorobenzotrifluoride	2-5-82	7-18-83	[d]	—	T
2-Chlorotoluene	5-22-81	4-28-82	[d]	—	T
Cresols	10-12-77		7-11-83	4-28-86	
Cumeme	11-29-84	—	11-6-85	Pending	c
Diethylene thiamine	5-22-81	—	4-29-82	5-23-85	c
Ethyl toluenes	5-25-82	—	5-23-83	5-17-85	T
Fluoroalkenes	11-25-80	6-4-84	11-6-85	Pending	c
Glycidol & derivatives	10-30-78	—	12-30-83 (ANPR)		c
Mesityl oxide	6-1-79	—	7-5-83	12-20-85	T
Oleylamine	12-14-83	—	11-19-84	Pending	
Phenylenediamines	5-28-80	—	1-6-86	Pending**	C

● Type C = carcinogenicity testing in 2-year bioassays; type T = tiered testing.
● *Decision not to test certain phenylenediamines. Others still under review.
aphas,l negotiated Testing Program completed. Data under review to determine further testing needs.
[b]Adequate environmental data submitted. Health testing needs under review. See footnote a.
[c]Industry ..rrentl, performing carcinogenicity bioassay under Negotiated Testing Agreement.
[d]Data adequate. Carcinogenicity testing not triggered.

SOURCE: EPA response toOTA request for information.

EPA may issue rules, under section 8(a), to require manufacturers, importers, and processors to provide information on production and uses of a chemical, plant characteristics, process characteristics, environmental releases, and worker exposures. Rules adopted under section 8(d) require that manufacturers, importers, and processors submit to EPA copies and lists of unpublished health and safety studies. (This is different from the general obligation under section 8(e) to notify EPA of studies revealing any "substantial risks." A section 8(d) rule requires the submission of all studies: positive and negative, "substantial risks" or not.)

Again, ITC recommendations have dominated EPA activity under these sections of TSCA. EPA has issued 8(a) and 8(d) rules for all the substances recommended by ITC, and in fact now routinely adds the chemicals from each new ITC report to the 8(a) and 8(d) lists within a few days after receipt of the report (108). Until 1986 there had been relatively few chemicals included under 8(a) and 8(d) that were not included in ITC reports. This may now be changing. For example, in the past year, 33 chemicals nominated by the Office of Solid Waste were added to the 8(d) list (320), and in May 1987 EPA published a final rule under section 8(d) that listed 107 chemicals nominated by the Offices of Toxic Substances, Water, and Solid Waste within EPA as well as by the CPSC (344). For section 8(a) rules in general, EPA has proposed a Comprehensive Assessment Information Rule, to establish uniform reporting requirements for chemicals that are subject to 8(a) rules. The proposal includes a list of 47 chemicals nominated by EPA's Air Office and Office of Toxic Substances, CPSC, OSHA, and NIOSH (308).

Under section 8(e) of TSCA, manufacturers, processors, and distributors of chemicals are required to notify EPA of information supporting the conclusion that a chemical "presents a substantial risk of injury to health or the environmerit. " Since January 1977 when this requirement became effective, EPA has received over 600 such notifications. In addition, EPA also receives "for your information (FYI)" notifications which do not fit the statutory requirements of section 8(e). The section 8(e) and FYI notifications are evaluated and EPA staff identify which chemicals should receive further attention, such as the prep-

aration of Chemical Hazard Information Profiles (CHIPS). The information provided in the 8(e) notices is made available to the interested public and is reported through the use of bulletins, published chemical status reports, and a computer database (341). Finally, EPA promulgated an 8(a) rule to update the information in the TSCA inventory of chemicals in commerce by requiring manufacturers and importers to report current data on production volume and plant site. The data in the original inventory was reported in 1977 and is out of date. Under the new rule the data must be reported every 4 years (335).

The various reporting requirements of TSCA have undoubtedly stimulated increased awareness in the chemical industry. Companies must evaluate information they obtain to determine whether it meets the notification requirements. Even if it does not, the information may be reported to EPA. To some extent, companies will voluntarily reduce exposures, conduct additional studies, change product labels and Material Safety Data Sheets (which provide information on product hazards and safe handling), and notify exposed workers, consumers, or others (341).

Existing Chemicals—Identified Hazards

For some existing chemicals, there may be enough information to determine that they cause cancer. For these chemicals, the issues are determining whether this risk of cancer is "unreasonable" and whether actions are needed to reduce or eliminate these risks. Table 3-19 lists 40 substances or groups of substances that EPA's Office of Toxic Substances has identified as carcinogenic, based on information provided to OTA. EPA has prepared hazard analyses and/or risk assessments for 25 of those substances.

This list does not cover all the substances for which TSCA evaluations, such as CHIPS, have been prepared. A CHIP provides a concise summary of available information on a chemical, including physical and chemical properties, estimates of exposure and environmental fate, health effects, environmental effects, and existing standards and recommendations. As of March 1987, CHIPS have been prepared for 93 different chemicals with carcinogenic concerns (336). CHIPS are initiated when EPA receives information on potential hazard from NTP bioassays, published scientific papers, or submissions to EPA under section 8(e). Using the information in a CHIP, EPA's Office of Toxic Substances may decide to develop more information on exposures, refer the chemical to other agencies or EPA programs, or begin action under TSCA.

EPA provided OTA with limited information about the kinds of evidence used for these identifications and risk assessments; most have relied on animal data. From the list in table 3-19, only asbestos and certain aromatic amines are known to be carcinogenic from human studies. The remainder are based on animal data, including 15 tested in NCI/NTP bioassays.

Regulatory actions for this group of existing chemicals consist of 4 designations under section 4(f) for an expedited review (4,4'-methylene dianiline, 1,3-butadiene, formaldehyde, and methylene chloride), 10 proposed or final SNURs for existing chemicals, and proposed section 6 regulatory actions for 4 substances.

The first section 4(f) designation, for 4,4'-methylene dianiline, occurred in 1983. Formaldehyde, designated in May 1984, had been considered in 1982 for designation. John Todhunter, the first director of the Office of Pesticides and Toxic Substances in the Reagan Administration, however, decided against designation—a controversial decision at the time. Following a lawsuit by NRDC, EPA formally acknowledged that section 4(f) applied to formaldehyde and announced a regulatory investigation in an ANPRM (158).

EPA response to its evaluation of chemicals under section 4(f) has been to refer chemical exposures limited to the workplace to OSHA under a provision of TSCA (sec. 9) that provides for referrals if EPA believes that OSHA, may be able to address the hazard. This has happened for acetaldehyde, acrylamide, chloromethane, 4,4-methylene bis (2-chloroaniline), toluenediamine, 4,4'-MDA, 1,3-butadiene, and for the occupational exposures associated with formaldehyde (see table 3-19). EPA is still investigating risks associated with nonoccupational exposure to formaldehyde in pressed wood products. The section 4(f) find-

Table 3-19.—TSCA: Existing Chemicals Identified as Carcinogens

Name	Hazard/risk assessment	Action
Acetaldehyde	Yes	Section 9 referral to OSHA
Acrylamide	Yes	Section 9 referral to OSHA; section 6 designation
Acrylates		SNUR for new acrylates under consideration
II-Aminoundecanoic acid		SNUR issued
Aniline	Yes	ANPR for testing
Aromatic amines		
Asbestos	Yes	Section 6: rules on asbestos removal: proposed ban/ phase-down
1,3-Butadiene [a]	Yes	Section 4(f) designation; section 9 referral to OSHA
Clarified slurry oil		
Chlorinated paraffins[a]	Yes	
Chloromethane	Yes	Section 9 referral to OSHA
3-Chloro-2-methylpropene (CMP)[a]	Yes	
C.I Disperse Yellow 3a		
D&C Red 9[a]		
1,4-Dichloro-2-butene (DCB)	Yes	EPA has taken no action because use is in closed systems
1,4-Dichiorobenzene [a]	Yes	
Dihydro safrole		
Epichlorohydrin		Proposed SNUR
Ethanolamines & metalworking fluids	Yes	Advisory warnings; section 6 proposal
Etheylenediaminetetra methylenephosphonic acid		
Formaldehyde	Yes	Section 4(f) designation; termination of investigation &section 9 referral to OSHA for occupational exposures
Glycol ethers	Yes	Section 9 referral to OSHA
Hexachlorobenzene (HCB)	Yes	SNUR & 8(a) rules issued
Hexachloronorbornadiene (HexBCH)	Yes	SNIJR & 8(a) rules issued
Hexafluoropropylene oxide		Proposed SNUR
Hexamethyl phosphoramide (HMPA)		SNUR issued
4,4-Methylenebis (2-chloroaniline)	Yes	SNUR proposed, section 8(a) rule issued. Section 9 referral to OSHA
Methylene chloride[a]	Yes	Section 4(f) designation
4,4'-Methylenedianiline [a]	Yes	Section 4(f) designation; section 9 referral to OSHA
Naptha solvent		
2-Nitropropane	Yes	
Paradichlorobenzene	Yes	Advisory warning
Pentachloroethane (PCE)[a]		SNUR issued; 8(d) rule
Perchloroethylene (perc)[a]	Yes	Decision not to designate under 4(f)
Phthalates		
DEHP[a]	Yes	
Polychlorinated biphenyls[b]		Section 6 rules
Propylene oxide[a]	Yes	EPA's quantitative risk assessment indicates risk is low
Toluenediamine	Yes	Advisory warning, section 9 referral to OSHA
Urethane		SNUR issued
Vinvlcyclohexene [a]		

[a] Tested by NCI/NTP.
[b] N,t in "Part 2 Summary," but regulated byEPA under TSCA.

SOURCE: EPA,OTS, "Part 2: Summary Narratives of Chemical Dispositions, "in EPA response to OTA request for information on substances identified as carcinogenic

ing for methylene chloride initiated an interagency regulatory investigation of hazards associated with methylene chloride and five other chlorinated solvents. All four designations under section 4(f) are based on results of animal studies.

After EPA issues a SNUR, a manufacturer must notify EPA before beginning production that falls under the terms of the SNUR. If EPA receivessuch notice, it can take action under section 5(e) or 5(f) to impose controls or prohibit production.

SNURs can be based on concern for any of the health and environmental effects regulated under TSCA, including carcinogenicity. Table 3-21 lists the existing chemicals for which carcinogenicity

Table 3-20. -TSCA: 4(f) Reviews

	4(f) Notice of accelerated review	ANPR summarizing evidence	Final action
4,4' -Methylene dianiline	4/27/83	9/20/83	7/5/85—Section 9(a) referral to OSHA
1,3-Butadiene.	1/5/84	5/15/84	10/10/85—Section 9(a) referral to OSHA
Formaldehyde	11/18/83	5123184	3/19/86—Announced termination of investigation concerning occupational exposures; non-occupational exposures still being investigated
Methylene chlori de.	5/14/85	10/1 7/85	Pendina

SOURCE: EPA response to OTA request for information

was one reason for the SNURs. The table shows that for existing chemicals considered to be carcinogenic, EPA began proposing SNURs in 1984, nearly 7 years after enactment of TSCA.[16] The table shows that EPA has proposed six SNURs (for eight chemicals) and issued four final SNURs on chemical substances of carcinogenic concern. For Hex-BCH it also issued a section 8(a) rule requiring reporting of production volumes. EPA issued an 8(a) rule for MBOCA instead of an SNUR. (See table 3-21.)

Section 6 provides wide-ranging authority to limit production and uses, which includes banning substances. Table 3-22 presents EPA actions concerning carcinogens under this section. Congress prohibited the manufacture of PCBs in the act itself, and required that EPA issue rules concerning their use and disposal.

EPA also issued rules in 1982 concerning identification and notification of asbestos in school buildings. In 1987, EPA proposed to require removal of this asbestos in certain circumstances. EPA has also issued rules to regulate the exposures of asbestos-removal workers who are not covered by OSHA standards. In 1986, EPA issued a proposal concerning asbestos, including proposed bans of certain asbestos applications (for which EPA has concluded there are available substitutes) and to "phase down, " over 10 years the amount of asbestos that may be mined or imported. That proposal has not been issued in final form.

[16]The total number of SNURS issued for carcinogenic and other concerns is 9 proposed (for 11 chemicals) and 8 final.

One other group of substances—chlorofluorocarbons (CFCs)—have been acted on under section 6. EPA banned use of CFCS as aerosol propellants and in 1980 issued an ANPRM concerning a possible limit on production and consumption of these substances for other uses, which may harm the ozone layer. That harm might have large consequences on the earth's climate, as well as increasing the amount of ultraviolet radiation reaching the earth's surface. Increased ultraviolet exposure would lead to an increase in the rate of skin cancer; thus CFCs in the atmosphere might, indirectly, be considered carcinogens. If further regulations or control of CFCs are proposed, such actions will not be proposed under TSCA, but rather, under section 157(b) of the CAA (47).

Another section 6 action that has not been *is*sued in final form is a 1984 proposal concerning certain potentially carcinogenic compounds that may form in metalworking fluids.

Table 3.21 .—TSCA: Existing Chemicals, Significant New Use Rules for Carcinogens

Name	Proposed	Final
Epichlorohydrin	1-2-87	—
Hexachloronorbornadiene (HEX-BCH)	2-22-85	1 l-19-85[a]
Hexafluoropropylene oxide	1-2-87	—
Hexa methylphosphoramide (HMPA)	10-10-84	3-19-86
4,4' -Methylenebis (2-chloroamiline)	4-26-85	4-18-86[b]
Pentachloroethane.	3.24-86	9-9-&36
Trichlorobutylene oxide	1-2-87	—
Urethane	10-10-84	3-19-86

[a]SNuR and section 8(a) rule.
[b]issued as section t3(a) rule.
SOURCE: EPA response to OTA request for information.

Table 3-22.—TSCA: Existing Chemicals; Section 6 Actions

Substance	Regulation	ANPRM	NPRM	Final
Asbestos	Statement of policy on coordination of regulatory activities	10-17-79		
Asbestos	Asbestos in schools: identification and notification		9-17-80	5-27-82
Asbestos	Asbestos abatement projects/worker protection		7-12-85	4-25-86 2-25-87 (revised final)
Asbestos	Mining and import restrictions and manufacturing; importation and processing prohibitions (asbestos ban & phase out)		1-29-86	
CFCS*	Prohibition of several uses		5-13-77	3-17-78
CFCS*	Production restriction	10-7-80		
Metalworking fluids	Prohibition of nitrites in		1-23-84	pending
PCBS.	Ban rule			5-31-79
PCBS	Exclusions, exemptions, and use authorizations for PCBs under 50 ppm		12-8-83	7-10-84
PCBs	Electrical equipment		4-22-82	8-25-82
PCBs	Use in closed and controlled waste manufacturing processes		6-8-82	10-21-82
PCBs	Amendment to use authorization for PCB railroad transformers		11-18-81	1-3-83
PCBs	Approval for PCB disposal facilities (procedural amendment)	3-30-83	11-17-83	3-30-83 7-10-84
PCBs	Use in microscopy and R&D proposed rule			
PCBs	Manufacture, processing, distribution in commerce exemptions		11-1-83	7-10-84
PCBs	Policy for compliance and enforcement of PCB storage for disposal regulation	11-17-83		11-17-83

● Not a carcinogen, but possible effects of CFCs on atmospheric ozone might increase skin cancer rates.

SOURCE: EPA response to OTA request for information.

EPA REGULATORY ACTIONS UNDER RCRA

The Resource Conservation and Recovery Act of 1976 was enacted to protect health and the environment from chemical wastes and to conserve material resources. Subtitle C of RCRA establishes a hazardous waste management system. EPA has issued regulations on the identification and listing of hazardous wastes, established recordkeeping and reporting requirements for generators, transporters, storers, and disposers of hazardous wastes, and permit requirements for treatment, storage, and disposal of hazardous waste. EPA requirements also establish a manifest system for tracking the movement of wastes from generation to disposal.

Wastes are subject to regulation under RCRA if they have the characteristics of hazardous waste, if they are listed as hazardous wastes, or if they are mixtures containing listed hazardous wastes. EPA did not include carcinogenicity and other acutely toxic effects among the characteristics of a hazardous waste, but instead regulates these substances through the listing mechanism. According to EPA, the test protocols for such characteristics are either insufficiently developed or too complex and dependent on the use of highly skilled personnel and specialized equipment to place the burden on generators of the waste (288). Among the characteristics, however, is "Extraction Procedure (EP) Toxicity." This provision specifies the maximum amount of 14 particular contaminants that may be found in a waste using a specific detection method. Most of the 14 contaminants are carcinogens.

A solid waste may be listed as a hazardous waste if it exhibits the characteristics of hazardous waste, if it is acutely hazardous, or if it contains toxic constituents listed in 40 CFR Appendix VIII. Carcinogenicity is one of the criteria for

listing a chemical in Appendix VIII (107,221). In May 1980, EPA published three generic lists of wastes considered to be hazardous and subject to the RCRA Subtitle C hazardous waste management regulations (40 CFR 261.31-40 CFR 261.33).

EPA's lists contain 361 commercial chemicals and 85 industrial waste processes, with others proposed as additions (not including Appendix VIII). Where possible, EPA emphasized waste streams from commercial processes, rather than specific hazardous substances to relieve waste generators of testing burdens and uncertainties in "relating a waste containing many substances to a list of specific substances" (290). Appendix VIII includes 391 constituents of the listed commercial compounds; many of them are carcinogens. The distinction between carcinogenicity and acute toxicity or other chronic health effects was not of particular concern to EPA when the list was compiled, since all of these criteria were used as the basis for the Appendix VIII listing.

Any listed waste is subject to RCRA "proper handling" regulations unless it is "delisted." Delisting a substance requires a petition for a regulatory amendment and is subject to requirements for public notice and comment. Although the Appendix VIII list of hazardous constituents is nonregulatory, inclusion of a substance on it may provide the basis for listing a commercial chemical product on the regulatory list. Waste generators may also be required to monitor groundwater for the constituents as a condition of their permits.

RCRA was passed in 1976. Congress gave EPA 18 months from the date of passage to provide criteria for characteristics of hazardous wastes and to list hazardous wastes. EPA issued its proposed rules on these topics in December 1978. In May 1980, it issued its first final rule concerning lists and characteristics of hazardous wastes (some other regulations are to follow). Also in 1980, EPA issued final rules for "proper handling" of hazardous wastes.

EPA has had considerable difficulty in adding to the list of hazardous wastes. Since issuing its list of 361 commercial chemicals and 85 industrial waste processes as well as the 4 generic waste characteristics in 1980, EPA has added 5 additional wastes, and no new characteristics. Moreover, EPA does not know whether the existing lists cover 90 percent of potentially hazardous wastes or 10 percent. Some of the as yet unlisted wastes are highly toxic, such as certain pesticides and known carcinogens (200).

Congress, in the 1984 RCRA amendments, addressed a number of aspects of the solid waste program. Relevant to this discussion of regulating chemicals for carcinogenicity were a series of congressional deadlines for EPA action and automatic bans on land disposal (known as "hammers") for particular, specified wastes if EPA fails to act by the deadlines for issuing treatment standards. The 1984 amendments also required that EPA review its waste list in three stages (ending in 1990) and decide whether to ban land disposal of these wastes (334).

EPA REGULATORY ACTIONS UNDER CERCLA

While RCRA was prospective—designed to prevent problems from hazardous wastes in the future—the Comprehensive Environmental Response, Compensation, and Liability Act of 1980, also known as "Superfund," was designed to address the cleanup of inactive hazardous waste sites, manage emergency response to the release of hazardous substances into the environment, and provide for liability and compensation. CERCLA addresses problems ranging from spills requiring immediate responses, to hazardous waste dumps leaking into the environment and posing long-term health and environmental hazards.

The list of hazardous substances is established under section 101(14) of CERCLA. Section 102 of CERCLA authorizes EPA to list additional hazardous substances—those substances which, "when released into the environment may present substantial danger to the public health or welfare or the environment. " Also, EPA is to set "report-

able quantities" (RQs) for all of these substances. The RQs are set by statute at 1 pound except when different reportable quantities have been set under section 311(b)(4) of the Clean Water Act. EPA is authorized to adjust RQs by regulation (42 U.S.C. 9602). Section 103 sets requirements notifying appropriate government officials in the event that a hazardous substance is released in amounts greater than the relevant RQ.

"Hazardous substances" under section *101(14)* of CERCLA include substances specified by sections 307 and 311 of the Clean Water Act, section 3001 of the Resource Conservation and Recovery Act, section 112 of the Clean Air Act, and section 7 of the Toxic Substances Control Act, and any substance designated as hazardous under section 102 of CERCLA (42 U.S.C. 9602). Of the CERCLA hazardous substances, 191 were identified as "potential carcinogens" (table 3-23).[17]

In 1985, EPA issued a final rule that clarified reporting procedures and set final RQ adjustments for 340 substances from its list of 717 hazardous substances (307). In 1986, EPA finalized RQ adjustments for an additional 102 hazardous substances (316). These adjustments did not cover potential carcinogens. In March 1987, EPA proposed RQ adjustments for the 191 substances identified as potential carcinogens on the CERCLA list (314).

To identify potential carcinogens on that list, EPA used IARC monographs, the Annual *Report on Carcinogens (see* ch. 5), final EPA determinations on carcinogenicity for other regulatory programs, and determinations by EPA's Carcinogen Assessment Group. EPA then developed a hazard ranking for the CERCLA substances that appeared on these various lists of carcinogens. The hazard ranking is a method used to sort a list of potential carcinogens into levels of relative carcinogenicity, which may then be equated to RQ levels for notification purposes (314).

The hazard ranking consisted of both qualitative and quantitative evaluations. For the qualitative portion, the chemicals were grouped using the CAG weight-of-evidence classification scheme (see ch. 2 and below). For the quantitative assessment, a potency factor was estimated by EPA's Carcinogen Assessment Group. For this hazard ranking, each potential carcinogen was placed in one of three potency groups, based on the estimated dose required to induce cancer in 10 percent of a population exposed for 70 years. In the final step in the ranking, the qualitative weight-of-evidence and quantitative potency grouping are combined to yield a relative hazard ranking—high, medium, or low—for each chemical.

For this ranking, 191 chemicals were placed in the weight-of-evidence categories. Fourteen chemicals were placed in group A (sufficient human evidence), 8 in group B1 (limited human evidence, sufficient animal evidence), 102 in group B2 (sufficient animal evidence only), 20 in group C (limited animal evidence only), and 7 in group D (no evidence for carcinogenicity). Two more chemicals were given a range: one in groups B1 and B2, and one in groups B2 and C. Finally, for 37 chemicals, there were no data for directly determining their carcinogenicity, but these chemicals were either compounds of known carcinogenic metals (for example, compounds of arsenic, beryllium, cadmium, chromium, and nickel) or members of chemical families of known carcinogens (for example, PCBs) (56). Thus, most of the chemicals were classified based on animal evidence.

The final grouping, after combining weight-of-evidence and potency estimates, had 62 chemicals in the "high," 77 in the "medium," and 45 in the "low" hazard groups; 7 chemicals were not ranked because of lack of evidence for carcinogenicity.

CERCLA was enacted in 1980. Congress, perhaps aware regulatory agencies are sometimes slow in issuing regulations for toxic substances, put requirements in the statute itself; it specified toxic substances that were to be listed for CERCLA regulation by incorporating previously established lists, and it set reportable quantities for many of these substances at 1 pound until EPA issued more appropriate reportable quantities. As of today, EPA has not modified the reportable quantities for CERCLA carcinogens, although, as indicated above, these regulations have been proposed.

[17] The carcinogens on the CERCLA list were identified in a technical background document prepared by Environmental Monitoring Services Inc. (56) in support of the proposed rule to adjust the reportable quantities for carcinogens issued in March 1987 (314).

Table 3.23.—Substances Listed in CERCLA That Were Identified as Potential Carcinogens

2-Acetylamlnofluorene (Acetamide N-9H-fluoren-2-yl)
Acrylonitrile
Aldrin amitrole
Arsenic
  Arsenic acid
  Arsenic disulfide
  Arsenic pentoxide
  Arsenic trichloride
  Arsenic trioxide
  Arsenic trisulfide
  Cacidylic acid
  Calcium arsenate
  Calcium arsenite
  Cupric acetoarsenite
  Dichlorophenylarsine
  Diethylarsine
  Lead arsenate
  Potassium arsenate
  Potassium arsenite
  Sodium arsenate
  Sodium arsenite
Asbestos
Auramine
Azaserine
Aziridine
Benz (c) acridine
Benz (a) anthracene
Benzene
Benzidine and its salts
Benzo (b) fluoranthene
Benzo (k) fluoranthene
Benzo (a) pyrene
Benzotrichloride
Benzyl chloride
Beryllium
  Beryllium chloride
  Beryllium fluoride
  Beryllium nitrate
alpha-BHC
beta-BHC
gamma-BHC (Lindane)
Bis (2-chloroethyl) ether
Bis (chloromethyl) ether
Bis (2-ethylhexyl) phthalate
Cadmium
  Cadmium acetate
  Cadmium bromide
  Cadmium chloride
Carbon tetrachloride
Chlorambucil
Chlordane
Chlornaphazine
Chloroform
Chloromethyl methyl ether (technical grade)
4-Chloro-o-toluidine, hydrochloride
Chromium
  Ammonium bichromate
  Ammonium chromate
  Calcium chromate
  Chromic acid
  Lithium chromate
  Potassium bichromate
  Potassium chromate
  Sodium bichromate
  Sodium chromate
  Strontium chromate
Chrysene
Coke Oven Emissions
Creosote
Cyclophosphamide
Daunomycin
DDD
DDE
DDT
Diallate
Diaminotoluene (mixed)
Dibenz (a,h) anthracene
1,2:7,8-Dibenzopyrene
1,2-Dibromo-3-chloropropane
3,3-Dichlorobenzidine
1,2-Dichloroethane
1,1 -Dichloroethylene
Dieldrin
1,2,3,4-Diepoxybutane
1,2-Diethylhydrazine
Diethylstilbestrol
Dihydrosafrole
3,3- Dimethoxybenzidine
Dimethyl sulfate
Dimethylaminoazobenzene
7,12 -Dimethylbenz (a) anthracene
3,3- Dimethylbenzidine
Dimethylcarbamoyl chloride
1,1-Dimethylhydrazine
1,2-Dimethylhydrazine
Dinitrotoluene (mixed)
2,4-Dinltrotoluene
2,6-Dinitrotoluene
1,4-Dioxane
1,2-Diphenylhydrazine
Epichlorohydrin
Ethyl carbamate (urethane)
Ethyl 4,4-Dichlorobenzilate
Ethylene dibromide
Ethylene oxide
Ethylenethiourea
Ethyl methanesulfonate
Formaldehyde
Glycidylaldehyde
Heptachlor
Heptachlor epoxide
Hexachlorobenzene
Hexachlorobutadiene
Hexachloroethane
Hydrazine
Indeno (1,2,3-cd) pyrene
Isosafrole
Kepone
Lasiocarpine
Lead acetate
Lead phosphate
Lead subacetate
Melphalan
Methyl chloride
3- Methylcholanthrene
4,4-Methylenebis (2-chloroaniline)
Methyl iodide
n-Methvl-n-nitro-n -nitrosoguanidine
Methylthlouracfl
Mitomycin C
1 -Naphthylamine
2-Naphthylamine
Nickel
  Nickel ammonium sulfate
  Nickel carbonyl
  Nickel chloride
  Nickel cyanide
  Nickel hydroxide
  Nickel nitrate
  Nickel sulfate
2-Nitropropane
n- Nitrosodi-n-butylamine
n- Nitrosodiethanolamine
n- Nitrosodiethylamine
n- Nitrosodimethylamine
n- Nitrosodi-n-propylamine
n- Nitroso-n-ethylurea
n- Nitroso-n-methylurea
n- Nitroso-n-methylurethane
n- Nitrosomethylvinylamine
n- Nitrosopiperidine
n- Nitrosopyrrolidine
5- Nitro-o-toluidine
Pentachloroethane
Pentachloronitrobenzene
Pentachlorophenol
Phenacetin IARC (H)
Polychtorinated biphenyls (PCBs)
  Aroclor 1016
  Aroclor 1221
  Aroclor 1232
  Aroclor 1242
  Aroclor 1248
  Aroclor 1254
  Aroclor 1260
1 ,3-Propane sultone
1 ,2-Propylenimine
Saccharin
Safrole
Selenium sulfide
Streptozotocin
2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD)
1,1, 1,2-Tetrachloroethane
1, 1,2,2-Tetrachloroethane
Tetrachloroethylene
Thioacetamide
Thiourea
o-Toluidine
p-Toluidine
o-Toluidine hydrochloride
Toxaphene
1,1,2-Trichloroethane
Trichloroethylene
Trichlorophenol (mixed)
2,4,5 -Trichlorophenol
2,4,6 -Trichlorophenol
Tris (2,3-dibromopropyl) phosphate
Trypan blue
Uracil mustard
Vinyl chloride

SOURCE Notice of proposed rulemaking issued 3-16-87, *federal Register* 52:8140, *1987*

Moreover, most of EPA's activity has focused on adjusting the RQs of substances already on the list rather than adding to the list. The original list was issued in April 1985 and contained 698 chemicals (307). Since then, EPA has added 19 chemicals to the list which had been added to RCRA in January 1985 (291) bringing the total to 717.

Several sections of the 1986 Superfund Amendments and Reauthorization Act (SARA) pertain to carcinogen testing and regulation. Section 121 requires that cleanup at Superfund sites "assures protection of human health and the environment" and achieves compliance with standards established under other Federal and State environmental laws (including the MCLGs of the new SDWA amendments, formerly called RMCLs, which are zero for carcinogens).

Section 110 requires the Agency for Toxic Substances and Disease Registry (ATSDR) of the Centers for Disease Control to compile a list of substances commonly found at Superfund sites and to prepare toxicological profiles of those substances. The first such list was issued on April 17, 1987 (306), and was drawn from the 717 substances already listed as hazardous under CERCLA. ATSDR must also initiate a testing program in cooperation with NTP to determine the health effects of substances on the list for which there are not adequate data. The type of testing required is within the discretion of ATSDR, but the agency must consider recommendations of the Interagency Testing Committee established under TSCA. EPA is required to issue regulations under TSCA to recover the costs of testing from the responsible parties. ATSDR must also prepare health assessments for Superfund sites included on the National Priorities List established by EPA and other sites in response to petitions from affected citizens.

Section 313 of Title III of SARA which is the Emergency Planning and Right to Know Act requires companies to report annually to EPA on the amounts of certain substances used and discharged into various media such as air and water. These substances are listed in Committee Print 99-169 of the Senate Committee on Environment and Public Works. EPA may add a substance to this list if it causes or can reasonably be anticipated to cause ". . . various chronic human health effects, " including cancer.

EPA'S CARCINOGEN ASSESSMENT GROUP

At EPA, risk assessment and risk management activities are separated more clearly than they are at several other agencies. The Carcinogen Assessment Group (CAG) was established in 1976 to centralize the conduct of risk assessments at EPA. CAG is organizationally independent from EPA's program offices (such as the air and water programs). Its personnel are responsible only for risk assessment, not risk management. CAG develops most risk assessments of carcinogens at EPA, although the Office of Pesticides and Toxic Substances (administering FIFRA and TSCA) usually conduct their own.

The first chemical given a quantitative risk assessment at EPA was vinyl chloride, which was assessed in 1975 for the Air Program. In its early years, CAG worked on a number of pesticides, including Chlordane/Heptachlor, Toxaphene, Lindane, and Endrin. In 1977, work began on assessment of airborne carcinogens, and in *1978* the development of the risk assessments for the water quality criteria documents began. The latter were published in draft form in three installments in 1979, and in final form in November 1980. Between the draft and final versions, CAG abandoned the one-hit model for extrapolating from high doses to low doses in favor of the linearized multistage model.

A full CAG risk assessment represents a thorough review and evaluation of the carcinogenic risks of a particular substance and averages 200 pages in length. These assessments include those prepared for the water quality criteria documents and the health assessment documents for EPA listing of hazardous pollutants under CAA. Other risk assessments are much shorter, such as the Health and Environmental Effects Profiles (HEEPs) prepared to support decisions to list sub-

stances under RCRA (typically, 30 to 40 pages) or to develop reportable quantities for hazardous substance releases under CERCLA (10 to 20 pages) (164).

Table 3-24 lists the substances for which the full assessments were performed. These assessments are all extensively reviewed, For hazard identification, CAG indicates the level of evidence in humans and animals, as well as the overall grouping in EPA's classification scheme (see ch. 2). CAG also performs dose-response assessments to calculate the estimated carcinogenic potency. The slope of the dose-response line is also presented in table *3-24.* When using data from animal studies, EPA estimates the upper confidence limit of the slope of the dose-response curve as derived from the multistage model (see ch. 2). Calculations based on human epidemiologic data are best estimates using a linear nonthreshold model. The slope represents the degree of carcinogenic response associated with a given exposure. The greater the slope, the more potent the carcinogen. Thus exposure to a relatively potent carcinogen (such as tetrachlorodibenzo-p-dioxin (TCDD)) will lead to a much higher probability of cancer than exposure to the same amount of a less potent carcinogen (for example, epichlorohydrin).

To date, CAG includes 57 chemicals in the list of full assessments complete with calculated potencies. Most of these have relied on animal data. Of the CAG list, nine were judged to have sufficient evidence in humans and eight of these nine (all except arsenic) also had sufficient evidence in animals. Three more were sufficient in animals with limited evidence in humans, while 37 were sufficient in animals with inadequate evidence in humans. The remaining seven were grouped in EPA classification C because the evidence was inadequate in humans and limited in animals .18 Additional substances have been evaluated by CAG at the request of EPA program offices, but have not received the level of review of the 57 listed in table 3-24.

[18]The total is only 56 because technical grade hexachlorocyclohexane is not classified, although 3 isomers of this chemical are.

OFFICE OF MANAGEMENT AND BUDGET

During the *1970s,* a series of executive orders gave groups in the Executive Office of the President a role in reviewing regulatory proposals. Over time this centralized review has greatly increased, culminating in extensive involvement in regulation by the Office of Management and Budget (OMB) under the Reagan Administration (219). OMB's role has been quite controversial.

President Reagan made "regulatory relief" an important goal for his administration early in 1981, and has issued two Executive orders on this subject. Executive Order 12291, issued February 17, 1981, requires that agencies prepare "regulatory impact analyses" on all major regulations, and requires that "regulatory action shall not be taken unless the potential benefits to society for the regulation outweigh the potential costs." It further specified that "regulatory objectives shall be chosen to maximize the net benefits to society" and required, to the extent possible, that all benefits and costs be quantified in monetary terms. This Executive order also centralized regulatory review in OMB and required agencies to submit proposed and final regulations and regulatory impact analyses prior to publication. Although the legal authority to propose and issue regulations remains with the heads of regulatory agencies, in practice Executive Order 12291 has required agencies to receive approval from OMB prior to publication (219).

Executive Order 12498 (issued January 4, 1985) primarily requires each agency subject to Executive Order 12291 to submit an annual agenda of "significant regulatory actions" to OMB. OMB also reviews **agency** regulations and research proposals for compliance with the Paperwork Reduction Act (Public Law 96-511).

Proponents of OMB review argue that presidents have always taken steps they thought nec-

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Table 3.24.—Substances Evaluated by the EPA Carcinogen Assessment Group for Carcinogenic Potency as of Aug. 1, 1986

Compounds	Level of evidence[a] Humans	Animals	Grouping based on EPA criteria	Slope[b] (mg/kg/day)$^{-1}$
Acrylonitrile	L	S	B1	0.24(W)
Aldrin	I	S	B2	16
Allyl chloride	I	S	B2	$1.19X10^{-2}$
Arsenic	S	I	A	15(H)
B[a]P		S	B2	11.5
Benzene	A	S	A	$2.9x10^{-2}$(W)
Benzidene	S	S	A	234(W)
Beryllium	I	S	B2	8.4(W)
I,3-Butadiene	I	S	B2	1.8(I)
Cadmium	L	S	B1	6.1(W)
Carbon tetrachloride	I	S	B2	$1.3OX1O^{-1}$
Chlordane	I	S	B2	1.3
Chlorinated ethanes				
1,2-Dichloroethane (Ethylene dichloride)	I	S	B2	9.1 X10-2
Hexachloroethane	I	L	c	$1.42x10^{-2}$
1,1,2,2-Tetrachloroethane	I	L	c	0.20
1,1,2-Trichloroethane	I	L	c	$5.73X10^{-2}$
Chloroform	I	S	B2	8.1 x10-2
Chromium VI	S	S	A	41(W)
Coke oven emissions	S	S		2.16(W)
DDT	I	S	B2	0.34
3,3-Dichlorobenzidine	I	S	B2	1.69
1,1-Dichloroethylene (Vinylidene chloride)	I	L	c	1.16(I)
Dichloromethane (Methylene chloride)	I	S	B2	$1.4X1O^{-2}$(I)
Dieldrin	I	S	B2	20
2,4-Dinitrotoluene	I	S	B2	0.31
Diphenylhydrazine	I	S	B2	0.77
Epichlorohydrin	I	S	B2	$9.9X10^{-3}$
Bis (2-chloroethyl) ether	I	S	B2	1.14
Bis (chloromethyl) ether	S	S	A	9300(1)
Ethylene dibromide (EDB)	I	S	B2	41
Ethylene oxide	L	S	B1	3.5 X1 O-'(I)
Heptachlor	I	S	B2	4.5
Heptachlor expoxide	I	S	B2	9.1
Hexachlorobenzene	I	S	B2	1.67
Hexachlorobutadiene	I	L	c	$7.75X10^{-2}$
Hexachlorcyclohexane technical grade				2.0
alpha isomer	I	S	B2	2.7
beta isomer	I		c	1.5
gamma isomer	I	S-L	B2-C	1.1
Hexachlorodibenzodioxin		S	B2	6.2x10+'
Nickel refinery dust	S	S	A	0.84(W)
Nickel subsulfide	S	S	A	1.7(W)
Nitrosamines				
Dimethylnitrosamine	I	S	B2	25.9(not by q_1^*)
Diethylnitrosamine	I	S	B2	43.5(not by q_1^*)
Dibutylnitrosamine	I	S	B2	5.43
N-nitrosopyrrolidine	I	S	B2	2.13
N-nitroso-N-ethylurea	I	S	B2	32.9
N-nitroso-N-methylurea	I	S	B2	302.6
N-nitroso-diphenylamine	I	S	B2	4.92x10-'
PCBs	I	S	B2	4.34
Tetrachlorodibenzo-p-dioxin (TCDD)				1.56x10+'
Tetrachloroethylene (Perchloroethylene)	I	S	B2	5.1 X10-2
2,4,6-Trichlorophenol	I	S	B2	$1.99X10^{-2}$
Toxaphene	I	S	B2	1.13
Trichloroethylene	I	S	B2	1.1 X10-2
Unleaded gasoline vapor		S	B2	$3.5X10^{-3}$
Vinyl chloride	S	S	A	$1.75X10^{-2}$(I)

[a]S = Sufficient evidence: L - Limited evidence: I - Inadequate evidence.

[b]Animal slopes are 95% upper-bound slopes based on the linearized multistage model They are calculated based on animal oral studies, except for those indicated by I (animal inhalation), W (human occupational exposure), and H (human drinking water exposure) Human slopes are point estimates based on the linear nonthreshold model Not all of the carcinogenic potencies presented In this table represent the same degree of certainty. All are subject to change as new evidence becomes available The slope value is an upper bound in the sense that the true value (which is unknown) is not likely to exceed the upper bound and may be much lower, with a lower bound approaching zero. Thus, the use of the slope estimate in risk evaluations requires an appreciation for the implication of the upper bound concept as well as the "weight of evidence" for the likelihood that the substance is a human carcinogen

SOURCE: Environmental Protection Agency

essary to control executive branch agencies (38). Further, even in a technological age, not all decisions are technical ones, and regulatory decisions involving both technical and policy decisions should be subject to the President's oversight. OMB's role has also been supported as necessary to achieve reform of the regulatory process, ensure "good regulation, " reduce the costs of regulation, curb overzealous agencies, and gain control over a potentially expensive process. By reviewing regulations and requiring cost-benefit analysis, OMB forces agencies to confront problems of "covert redistribution and overzealous pursuit of agency goals, " thus making agencies accountable to the President (38).

But OMB's review of agency actions has generated criticism (206,208,225). These criticisms raise constitutional issues, other legal issues, and more public policy issues about OMB's role in reviewing agency decisions.

Even with presidentially delegated authority, it may be unconstitutional for OMB to control decisions delegated by Congress to executive branch agencies (152). Furthermore, if OMB, in reviewing and approving or disapproving regulations, uses considerations not authorized by statute, its actions may not be permissible, especially when this conflicts with expressed congressional intention (152). In addition, since congressional committees have documented some evidence of ex *parte* and secret contacts between OMB and regulated industries (206,225), several commentators suggest this undermines the Administrative Procedure Act's public participation requirements for informal rulemaking (132,153).

Critics have also argued that delays imposed by OMB

> . . . are paid for through the decreased health and safety of the American public . . .; [that OMB review] . . . places the ultimate rulemaking decisions in the hands of OMB personnel who are neither competent in the substantive areas of regulation, nor accountable to Congress or the electorate in any *meaningful sense* . . . [and that Executive Order 12498] . . . allows OMB to cut off investigations before they even begin, making it nearly impossible to attack OMB's decision that a potential rule is "unnecessary" (132).

One problem with the regulation of carcinogens discussed in this chapter involves delays in regulating problematic substances, delays between the time a statute is passed and the time an agency is authorized to regulate toxic substances, and delays between the time an agency has information that a substance is a carcinogen and the issuance of regulations. In recent years there have been additional delays because of OMB's review of major regulations.

EPA has compiled data on the average number of days rules are extended past the time limits specified by Executive Order 12291, for example, 30 days for a minor rule and 60 days for a major rule (one with an impact on the economy of $100 million or more).

> The average extension in April 1985 was slightly under 50 days; previous peaks were near 100 days . . . [thus] . . . OMB holds minor rules for an average of over two months [rather than the 10 days Executive Order 12291 specifies for minor rules] and major rules for over four months [rather than the 60 days specified by Executive Order 12291] (225).

This average conceals some much longer delays involving rules that generated considerable dispute between OMB and some of the regulatory agencies:

- EPA's proposed ban on certain uses of asbestos and its phase-out over time of most other uses of asbestos were delayed more than 1 year.
- OMB delayed by at least 5 months EPA's recommended maximum contaminant levels "for approximately forty organic and inorganic chemicals under the authority of the Safe Drinking Water Act . . .," leading Senator Durenberger to introduce an amendment to require OMB to complete its review of the RMCLs by a certain date.
- For EPA's proposed National Priorities List under Superfund, OMB forced EPA to choose between "delaying an entire executive action or sacrificing a part of it to gain OMB's approval of the major portion. "
- Eleven proposed New Source Performance Standards for new and modified stationary air pollution sources, all submitted to OMB 3 to 13 months ahead of a statutory dead-

line, were delayed beyond that time. Fourteen months of the delay in publishing these rules were due to OMB's review under Executive Order 12291.
- High-level radioactive waste storage rules proposed by EPA were delayed by 1 year, leading to a suit by the Environmental Defense Fund against both OMB and EPA for missing a statutory deadline. Several congressmen filed an amicus brief on the side of the Environmental Defense Fund (225).

Shortly after the report from the Senate Committee on Environment and Public Works was completed, the District Court for the District of Columbia ruled that OMB has no authority to delay the issuance of the final rule which was the subject of suit or to delay issuance of any other rules "subject to statutory or judicial deadlines under the Hazardous and Solid Waste Amendments of 1984" (225).

Under the Paperwork Reduction Act, OMB also reviews research proposals that involve government survey research. One example of OMB's involvement in a study concerning a carcinogen was a NIOSH proposal to evaluate the risk to human beings from MBOCA. This study was delayed by OMB for 6 months. This was not a regulation, but a proposed study of human beings, when NIOSH already had evidence that MBOCA was carcinogenic in three animal species (207). The Paperwork Reduction Act mandates that agencies obtain approval from OMB concerning these recordkeeping requirements. In some cases, regulations will require that records be kept by industry.

POSSIBILITIES FOR IMPROVING AGENCY TIMELINESS

This chapter has described the activities of the Federal agencies in assessing and regulating carcinogenic chemicals. A number of chemicals have been regulated for carcinogenicity and exposures have been reduced or eliminated. In some cases, the agencies have determined that the risks posed by particular chemicals are low and that there was no need to regulate. In other cases, the agencies are still obtaining toxicity and other information needed to regulate or are developing the analyses required by their statutes and by OMB. Finally, there probably are cases in which the necessary data have been collected, the analyses have been performed, and agency staff are simply waiting for decisions whether to regulate.

A constant in this chapter's overview of Federal activities is that the regulatory process is often a lengthy one.[19] To force regulatory action, Congress has legislated a variety of statutory mechanisms. These include statutory deadlines, congressionally mandated regulations, and institutional review and response mechanisms.

The most common of these have been statutory deadlines; although they have led to regulatory action, they are also frequently missed by the agencies. A report on the statutory deadlines in 15 environmental protection statutes affecting EPA found approximately 328 deadlines for setting regulations, issuing reports and studies, achieving compliance, setting guidelines, and accomplishing other tasks. The report estimated that 14 percent of these deadlines were actually met. However, while the original deadlines were missed, an estimated 41 percent of the EPA actions that were required had been completed by September 1985. The report concluded that, while statutory deadlines have brought about action by EPA and secured advances in environmental protection, deadlines are not sufficient to speed action. Moreover, Congress sets more deadlines for EPA than the Agency can meet, thus diluting the effectiveness of any one deadline, and it often sets unrealistic deadlines (48).

Congress has also mandated particular regulatory requirements. For example, in section 6 of the Toxic Substances Control Act, Congress ordered EPA to regulate the disposal of PCBs within 6 months and to prohibit further manufacture, except in closed systems, within 1 year of enactment.

[19] Concern about regulatory delay is not new. See, for example, a 1977 paper by Sidney Wolfe (364).

Another form of mandate is to require an agency to regulate a specified list of chemicals. For instance, in the Occupational Safety and Health Act, Congress ordered OSHA to adopt within 2 years established Federal occupational health and safety standards and the standards adopted by consensus standards organizations. In CERCLA, EPA was required to adopt a list of chemicals that had already been regulated under other environmental laws. In the 1977 Clean Water Act amendments, Congress codified a list of 65 classes of pollutants that had been developed for a consent decree settling a lawsuit directed against EPA for failing to regulate water pollutants. For the deadlines set in the 1984 RCRA amendments, Congress added "hammers' '-statutory bans that take effect if EPA misses deadlines; depending on one's perspective, this combines either the best and worst of these two approaches to congressional mandates.

One final mechanism is requiring agencies to consider or, stronger still, respond to recommendations of another agency or organization. For example, OSHA is to consider the recommendations of NIOSH when developing new occupational health and safety standards. Stronger is the requirement that the Mine Safety and Health Administration must respond within 60 days to NIOSH recommendations. However, NIOSH has not yet sent any recommendations to MSHA that trigger this requirement. Under TSCA, EPA must respond to ITC's nominations of chemicals for toxicity testing, although one possible response is a decision not to require testing. In fact, the lists of chemicals recommended by ITC have dominated EPA activities on the testing of existing chemicals.

In the Safe Drinking Water Act of 1974, Congress required EPA to commission a study on drinking water by NAS. The study was to identify potentially harmful contaminants in drinking water and make recommendations concerning national standards for maximum contaminant levels. It was expected that EPA would use those recommendations. However, the NAS study decided that it was not appropriate to recommend contaminant levels, concentrating instead on developing information on potential toxic effects. Later amendments to the SDWA removed the requirement for EPA response to the NAS reports.

None of these mechanisms is a panacea. Congressional deadlines and mandated lists may force action, but also may divert regulatory agencies from chemicals and regulations more in need of regulation. Lists, in particular, may immerse Congress in extensive detail on particular chemicals. An institutional mechanism allows a group of experts or a scientific agency to sort through the lists of particular chemicals and recommend the ones of highest priority. On the other hand, establishing regulatory implications may mean that the recommending group should have a formal process for decisionmaking, including response to public comments. Establishing such a process might slow the whole operation down. In addition, establishing a regulatory linkage might dissuade scientists from participating who do not want to be involved in decisions with regulatory implications. Finally, such recommendations may inappropriately redirect agency priorities and create pressure for regulatory action. Such regulatory action may not always be necessary and may impose costs on regulated industries.